

**IN THE UNITED STATES DISTRICT COURT FOR THE  
DISTRICT OF NEW JERSEY**

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IN RE: JOHNSON & JOHNSON	)	
TALCUM POWDER PRODUCTS	)	
MARKETING, SALES PRACTICES AND	)	MDL Docket No. 2738
PRODUCTS LIABILITY LITIGATION	)	

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This Document Relates To All Cases

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**DEFENDANTS JOHNSON & JOHNSON AND LLT MANAGEMENT,  
LLC'S MEMORANDUM OF LAW IN SUPPORT OF MOTION TO  
EXCLUDE PLAINTIFFS' EXPERTS' GENERAL CAUSATION OPINIONS**

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The peer-reviewed literature, medical organizations and U.S. governmental agencies have consistently agreed that the scientific evidence does ***not*** support the conclusion that talc is a cause of ovarian cancer.<sup>1</sup> Even the most recent developments on which plaintiffs and their experts hang their hats have confirmed that the relevant science has not established a causal link. Nonetheless, plaintiffs’ experts seek to opine at trial that “there is ***incontrovertible*** evidence” that cosmetic talc does in fact cause ovarian cancer<sup>2</sup>—i.e., that “genital use of talcum powder products presents a significant risk factor . . . for *all* women who use the products.”<sup>3</sup>

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<sup>1</sup> See Ovarian, Fallopian Tube, and Primary Peritoneal Cancer Prevention (PDQ®)—Health Professional Version, National Cancer Institute (“NCI 2024 PDQ”), <https://www.cancer.gov/types/ovarian/hp/ovarian-prevention-pdq> (last updated Mar. 6, 2024); Letter from Steven M. Musser, Ph.D., Deputy Dir. for Sci. Operations, Ctr. for Food Safety & Applied Nutrition, to Samuel S. Epstein, M.D., Cancer Prev. Coalition, Univ. of Ill. – Chi. School of Pub. Health, at 1 (Apr. 1, 2014) (“FDA Denial Letter”) (Ex. 1 to Decl. of Jessica Davidson (“Davidson Decl.”)); Ovarian Cancer Risk Factors, Centers for Disease Control and Prevention, <https://www.cdc.gov/ovarian-cancer/risk-factors/index.html> (last updated Oct. 26, 2023); Ovarian Cancer FAQs, American College of Obstetricians and Gynecologists, <https://www.acog.org/womens-health/faqs/ovarian-cancer> (last updated May 2022).

<sup>2</sup> (Dep. of Jack Siemiatycki (“3/27/24 Siemiatycki Dep.”) 226:22-24, Mar. 27, 2024 (Ex. 2 to Davidson Decl.) (emphasis added); 3d Am. Rep. of Jack Siemiatycki (“Siemiatycki 3d Am. Rep.”) at 63, 67-68, May 27, 2024 (Ex. 3 to Davidson Decl.).)

<sup>3</sup> (3d Am. Rep. of Judith Wolf (“Wolf 3d Am. Rep.”) at 21, May 28, 2024 (Ex. 4 to Davidson Decl.) (emphasis added); *see also, e.g.*, 3d Am. Rep. of Rebecca Smith-Bindman (“Smith-Bindman 3d Am. Rep.”) at 3, May 28, 2024 (Ex. (cont’d)

Judge Wolfson ruled in 2020 that because three of plaintiffs’ experts (Drs. Anne McTiernan, Daniel Clarke-Pearson and Arch Carson) all purported to apply the Bradford Hill framework for assessing causation, their opinions—which defied the scientific consensus—were nonetheless admissible and that their approach to scientific principles was a matter of “weight” that should be decided by jurors based on cross-examination. *See In re Johnson & Johnson Talcum Powder Prods. Mktg., Sales Pracs. & Prods. Litig.*, 509 F. Supp. 3d 116, 148, 163, 166-67, 172, 175 (D.N.J. 2020) (invoking the word “weight” no fewer than 55 times).<sup>4</sup>

This was not a correct application of Rule 702. Rather, as the recent

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5 to Davidson Decl.) (“Substantial evidence supports a strong positive statistically significant association between ovarian cancer and genital exposure to talcum powder products. Regular exposure . . . causes ovarian cancer in some women.”); 3d Am. Rep. of Anne McTiernan (“McTiernan 3d Am. Rep.”) at 27, May 28, 2024 (Ex. 6 to Davidson Decl.) (“[R]ecall bias’ is unlikely to be an issue.”); Rep. of Bernard L. Harlow (“Harlow Rep.”) at 6, Nov. 15, 2023 (Ex. 7 to Davidson Decl.) (“It is not plausible that recall bias can explain away the association.”).) This motion addresses the opinions being offered by the following experts: Drs. Arch Carson, Daniel Clarke-Pearson, Sarah Kane, Anne McTiernan, Patricia Moorman, Jack Siemiatycki, Sonal Singh, Ellen Blair Smith, Rebecca Smith-Bindman, Judith Wolf, Michele Cote and Bernard Harlow.

<sup>4</sup> At the beginning of her opinion, Judge Wolfson also noted that “the reasoning in this Court’s Opinion, applies with equal force to the remainder of the pending *Daubert* motions.” *In re Johnson & Johnson*, 509 F. Supp. 3d at 128-29. More recent cases explain that “each application [of Bradford Hill] is distinct and should be analyzed for reliability.” *In re Acetaminophen - ASD-ADHD Prods. Liab. Litig.*, MDL No. 3043, 2023 U.S. Dist. LEXIS 224899, at \*56 (S.D.N.Y. Dec. 18, 2023) (“*Acetaminophen I*”) (quoting *In re Zolof (Sertraline Hydrochloride) Prods. Liab. Litig.*, 858 F.3d 787, 795 (3d Cir. 2017)). Thus, the Court should have assessed each expert’s opinions separately.

amendments to Rule 702 have clarified, a “district court ha[s] an independent duty to ensure that all experts ‘reliably *applied*’ Bradford Hill.” *In re Onglyza (Saxagliptin) & Kombiglyze (Saxagliptin & Metformin) Prods. Liab. Litig.*, 93 F.4th 339, 347 (6th Cir. 2024) (emphasis added) (citing Fed. R. Evid. 702(d) (2011) (amended 2023)); *see also id.* at 347-48 (rejecting argument that “a ‘jury, not the trial judge, must evaluate and weigh conflicting expert testimony’” because “district courts may allow juries to evaluate and weigh *only* relevant and reliable expert testimony”) (citation omitted); *In re Acetaminophen – ASD-ADHD Prods. Liab. Litig.*, MDL No. 3043, 2024 U.S. Dist. LEXIS 121259, at \*83 (S.D.N.Y. July 10, 2024) (“*In re Acetaminophen IP*”) (rejecting “argu[ment] that a jury and not a court must determine whether Dr. Ness’s opinion on causation is correct” because “it is the task of the trial judge to ‘ensure that any and all scientific testimony . . . is . . . reliable’”) (quoting *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579, 589 (1993)). Application of that critical gatekeeping function requires exclusion of plaintiffs’ experts’ opinions because the experts distort epidemiology in a results-oriented manner and disregard longstanding concepts such as statistical significance. Moreover, plaintiffs’ experts do not meaningfully grapple with scientific evidence published since the parties’ original briefing undermining a causal relationship.

**First**, plaintiffs’ experts misapply the threshold consideration in the

Bradford Hill framework by claiming that a facially weak increased risk of ovarian cancer reported in some of the case-control studies is strong. These claims are particularly unreliable in light of more recent studies like O'Brien 2023 demonstrating that the very small reported relative risk is likely being driven by recall bias, thanks in part to extensive lawyer advertising that has scared women.

**Second**, plaintiffs' experts also seek to manufacture consistency across the epidemiologic literature by dismissing all of the cohort studies (which found no statistically significant association). While plaintiffs' experts contend that the cohort studies lack sufficient power, O'Brien 2020, published after the first round of expert discovery, is the largest epidemiologic study to ever assess the proposed relationship, and it, too, found **no** statistically significant association. Plaintiffs' experts also try to bolster their claims about consistency by disregarding statistical significance, pressing the same methodologically flawed approach to epidemiology that led to Drs. McTiernan and Moorman recently being excluded in the Zantac MDL litigation. *See In re Zantac (Ranitidine) Prods. Liab. Litig.*, 644 F. Supp. 3d 1075, 1222, 1234, 1237-39, 1242, 1254 (S.D. Fla. 2022) (criticizing Dr. McTiernan's "frequent reliance upon statistically insignificant data"; rejection of study authors' cautions and conclusions; practice of "selective[ly] disregard[ing] . . . data within a study that does not tend to support her conclusion"; and disregard for the consensus of "the scientific community"); *see*

*also id.* at 1253-55 (excluding Dr. Moorman’s similarly unreliable and “conclusion-oriented process” in assessing epidemiology).

**Third**, although plaintiffs’ experts largely agree that the studies (including one co-authored by Dr. Moorman) have **not** found a real dose-response relationship, they offer the result-oriented opinion that this factor should be given “lesser weight” in the causation analysis. This reasoning contravenes the elementary toxicological principle that the dose makes the poison.

Plaintiffs’ experts do not reliably apply the remaining Hill factors either. Experimental evidence does not support causation, and the experts’ opinions are incoherent with broader scientific knowledge, including the knowledge that genetic mutations are the established cause of cancer and that talc does not cause mutations. Plaintiffs’ experts also disregard the improbability that talc exposure causes different subtypes of ovarian cancer, which are essentially different diseases with different suspected etiologies.

Two recent developments touted by plaintiffs and their experts do not change the scientific landscape. O’Brien 2024—which relied on retrospective questionnaires and imputed data—expressly warned that its “results do **not** establish causality and do not implicate any specific cancer-inducing agent.”<sup>5</sup>

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<sup>5</sup> O’Brien, *Intimate Care Products and Incidence of Hormone-Related Cancers: A Quantitative Bias Analysis*, J. Clin. Oncol. (2024): JCO-23, at 13 (“O’Brien 2024”) (Ex. 8 to Davidson Decl.) (emphasis added).

Similarly, while the International Agency for Research on Cancer (“IARC”), an agency of the World Health Organization, recently reclassified talc as “probably carcinogenic to humans,” it made clear that “a causal role for talc could **not** be fully established” in light of “biases in how talc use was reported in the epidemiological studies.”<sup>6</sup> As Katie O’Brien (a member of the IARC working group and co-author of the two O’Brien studies just discussed) put it, “the human study evidence was **not** strong enough to say that talc causes ovarian cancer.”<sup>7</sup> Simply put, plaintiffs’ experts are not only reaching “conclusions the authors d[id] not make,” but are specifically contravening their express warnings **against** inferring causality. *In re Onglyza*, 93 F.4th at 346. This “betray[s] a lack of scientific rigor” that should be the end of this litigation. *Id.* (citation omitted).

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<sup>6</sup> Press Release No. 352, IARC, *IARC Monographs Evaluate the Carcinogenicity of Talc and Acrylonitrile*, IARC Monographs Volume 136 (July 5, 2024) (“IARC Press Release”), [https://www.iarc.who.int/wp-content/uploads/2024/07/pr352\\_E.pdf](https://www.iarc.who.int/wp-content/uploads/2024/07/pr352_E.pdf) (emphasis added). Because the IARC monograph with the new classification will not be published until some unspecified date in 2025, it is impossible to fully evaluate the decision-making process behind this change.

<sup>7</sup> Statement of Katie O’Brien, Science Media Centre Spain, <https://sciencemediacentre.es/en/talc-classified-probably-carcinogenic-humans-iarc> (last visited July 13, 2024) (“O’Brien Statement”) (emphasis added); *see also* Stayner, *Carcinogenicity of Talc and Acrylonitrile*, *Lancet Oncol.* (2024), at 2 (“Stayner 2024”) (Ex. 9 to Davidson Decl.) (summarizing IARC’s reclassification, which was based on “**limited**” evidence that talc causes ovarian cancer in humans” and cautioning that “bias from differential exposure misclassification could not be excluded based on a bias analysis conducted by the Working Group and confounding by asbestos contamination of the talc also could not be ruled out”) (emphasis added).

“[T]he role of the district court [is] to ‘function as a gatekeeper; it is not for the courts to be the pioneers, forging new trails in scientific thinking, especially when that means departing from well-established research principles.’”

*Acetaminophen I*, 2023 U.S. Dist. LEXIS 224899, at \*122.(citation omitted).

Admitting plaintiffs’ experts’ opinions that cosmetic talc is a cause of ovarian cancer would contravene Rule 702 and defy the consensus of the FDA and countless independent U.S. medical and scientific institutions that causation has not been established.

## **BACKGROUND**

### **A. Fundamental Epidemiological Principles**

The literature on talc and ovarian cancer is primarily divided into two kinds of studies (cohort and case-control). Cohort studies are prospective: they begin by identifying a large group of healthy women and follow them forward in time with regard to the agent and disease at issue.<sup>8</sup> Case-control studies, by contrast, are retrospective: they compare a group of women already diagnosed with ovarian cancer (cases) to a matched group of women without the disease (controls) and attempt to compare risk based on both groups’ recollection of their past talc use.<sup>9</sup>

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<sup>8</sup> (E.g., Rep. of Patricia G. Moorman (“Moorman Rep.”) at 7-8, Nov. 16, 2018 (Ex. 10 to Davidson Decl.).)

<sup>9</sup> E.g., *In re Johnson & Johnson*, 509 F. Supp. 3d at 161.

Scientists generally consider cohort studies to be more reliable than case-control studies due to the unique susceptibility of case-control studies to recall bias (i.e., the phenomenon that people with a disease are more likely to “remember” past exposures, whether they occurred or not) and confounding (i.e., that individuals with a disease may share other risk factors not accounted for in a study).<sup>10</sup>

Epidemiological studies generally report their results in terms of relative risks (“RR”), odds ratios (“OR”), or hazard ratios (“HR”). For purposes of evaluating general causation in this litigation, these are essentially interchangeable concepts that describe the increase (or decrease) in risk between exposure and disease.<sup>11</sup> This number can be reported using something called a point estimate—

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<sup>10</sup> See Penninkilampi & Eslick, *Perineal Talc Use and Ovarian Cancer: A Systematic Review and Meta-Analysis*, 29(1) *Epidemiology* 41, 47 (2018) (“Penninkilampi 2018”) (Ex. 11 to Davidson Decl.) (“The retrospective nature of case-control studies introduces the potential for recall bias”; case-control studies have “potential exposure misclassification issues” and are “low-level evidence.”). Penninkilampi is cited favorably by almost all of plaintiffs’ experts. (See, e.g., 3d Am. Rep. of Daniel L. Clarke-Pearson (“Clarke-Pearson 3d Am. Rep.”) at 9, May 28, 2024 (Ex. 12 to Davidson Decl.); Am. Rep. of Michelle Cote (“Cote Am. Rep.”) at 19-20, May 28, 2024 (Ex. 13 to Davidson Decl.); McTiernan 3d Am. Rep. at 64-66, 82-83, 98-99.)

<sup>11</sup> Wentzensen & O’Brien, *Talc, Body Powder, and Ovarian Cancer: A Summary of the Epidemiologic Evidence* 163 *Gynecol. Oncol.* 199, 202-03 (2021) (“Wentzensen & O’Brien 2021”) (Ex. 14 to Davidson Decl.) (“Both case-control studies and cohort studies typically report relative risk measures, including odds ratios or hazard ratios. These relative risks indicate how much the risk of an outcome is increased due to a specific exposure in one group compared to another.”).

an estimate “expressed as a single number.”<sup>12</sup> For instance, for the O’Brien 2020 results (HR: 1.09, 95% CI 0.99-1.17), the point estimate is 1.09.

An odds ratio of 1.0 means that the disease was found to occur no more frequently than in the general (referential) population.<sup>13</sup> An odds ratio of 2.0 means that the disease was found to occur twice as frequently (representing a 100% increased risk), and an odds ratio of 0.5 means the disease was found to occur half as frequently (representing a 50% decrease in risk).

In computing study results, epidemiologists provide a range of values, commonly referred to as a confidence interval, in order to determine whether their findings are statistically significant.<sup>14</sup> A confidence interval provides 95% certainty of the true risk estimate and is intended to ensure that scientists do not advance theories that are based on pure chance. If the confidence interval includes 1.0 (i.e., the possibility of no association), it cannot be said with 95% confidence that there is any association between the exposure and the outcome.<sup>15</sup>

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<sup>12</sup> *Reference Manual on Scientific Evidence* (“RMSE”) (3d ed. 2011), at 291.

<sup>13</sup> *See, e.g., RMSE* at 625, 627.

<sup>14</sup> (*E.g.,* McTiernan 3d Am. Rep. at 14.)

<sup>15</sup> (*Id.*)

**B. The Scientific Landscape At The Time Of The Prior Ruling**

***Cohort Studies.*** In the last 20 years, there have been four published studies reporting on the results of three large cohort studies (the Nurses' Health Study ("NHS"), Women's Health Initiative ("WHI") and Sister Study) examining the putative talc-ovarian cancer association. Taken together, those studies have followed more than **200,000 women** and collectively reached the same conclusion: ***perineal talc use does not elevate ovarian cancer risk.***<sup>16</sup>

***Case-Control Studies.*** In addition to the cohort studies, there have been approximately 35 case-control studies<sup>17</sup> on talc and ovarian cancer.<sup>18</sup>

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<sup>16</sup> See Gertig, *Prospective Study of Talc Use and Ovarian Cancer*, 92(3) J. Nat'l Cancer Inst. 249 (2000) ("Gertig 2000") (Ex. 15 to Davidson Decl.); Gates, *Risk Factors for Epithelial Ovarian Cancer by Histologic Subtype*, 171(1) Am. J. Epidemiol. 45 (2010) ("Gates 2010") (Ex. 16 to Davidson Decl.); Houghton, *Perineal Powder Use and Risk of Ovarian Cancer*, 106(9) J. Nat'l Cancer Inst. 1 (2014) ("Houghton 2014") (Ex. 17 to Davidson Decl.); Gonzalez, *Douching, Talc Use, and Risk of Ovarian Cancer*, 27(6) Epidemiology 797 (2016) ("Gonzalez 2016") (Ex. 18 to Davidson Decl.). Chang 2024, based on data reported in the Sister Study cohort, also reported a non-significant HR for vaginal talc use. See Chang, *Use of Personal Care Product Mixtures and Incident Hormone-Sensitive Cancers in the Sister Study: A U.S.-Wide Prospective Cohort*, 183 Environ. Int'l 1 (2024) ("Chang 2024") (Ex. 19 to Davidson Decl.).

<sup>17</sup> There are two types of case-control studies at issue: hospital-based studies, which generally gather "cases" of women who have ovarian cancer and "controls" who are hospitalized for other reasons; and population-based studies, in which the "cases" are women (often from a specified community) who have ovarian cancer and the "controls" are healthy women in the general population, who are typically selected by random telephone dialing.

<sup>18</sup> (See Wolf 3d Am. Rep. at 5.)

Approximately half of the case-control studies have not found a statistically significant association between talc use and ovarian cancer.<sup>19</sup> The remaining case-control studies report relatively weak risks of approximately 1.3.<sup>20</sup> None of these studies has taken the position that its findings, whether by their own force or in combination with other studies, prove a causal relationship between perineal talc use and ovarian cancer. To the contrary, individual studies—including studies authored by plaintiffs’ experts in talc litigation—have repeatedly expressed that their findings *do not* establish causation.<sup>21</sup>

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<sup>19</sup> See Penninkilampi 2018 at 46 fig. 2. (See also McTiernan 3d Am. Rep. at 36; Dep. of Patricia G. Moorman (“2/13/24 Moorman Dep.”) 93:1-23, Feb. 13, 2024 (Ex. 20 to Davidson Decl.) (“Q. So that means 11 out of 24 case-control studies did not show a significant association, right? A. Not a statistically significant increased risk, yes.”).)

<sup>20</sup> See Wentzensen & O’Brien 2021 at 199, 203; Micha, *Talc Powder and Ovarian Cancer: What is the Evidence?*, 306 Arch. Gynecol. Obstet. 931, 932 (2022) (“Micha 2022”) (Ex. 21 to Davidson Decl.) (“Several case-control studies have examined the relationship between talc use and ovarian cancer development, wherein an elevated risk (relative risk: 1.1-3.9) of developing ovarian cancer was reported, whereas alternative reports have not demonstrated a relationship.”) (citations omitted).

<sup>21</sup> See, e.g., Cramer, *Presence of Talc in Pelvic Lymph Nodes of a Woman With Ovarian Cancer and Long-Term Genital Exposure to Cosmetic Talc*, 110(2) Obstetrics & Gynecology 498, 500 (2007) (“Cramer 2007”) (Ex. 22 to Davidson Decl.) (case study co-authored by plaintiffs’ experts in talc litigation stating “we are not claiming that a causal relationship between ovarian cancer and talc use is proven for this case or in general”); Moorman, *Ovarian Cancer Risk Factors in African-American and White Women*, 170(5) Am. J. Epidemiology 598, 605 (2009) (“Moorman 2009”) (Ex. 23 to Davidson Decl.) (cautioning that “there is a clear need for additional studies in order to deepen our understanding of causative and protective factors in this population”).

**Meta-analyses.** A meta-analysis is a study that attempts to combine information from multiple previous studies and provide a “summary” point estimate and confidence interval.<sup>22</sup> Meta-analyses have generally reported an overall relative risk of approximately 1.3, but the 1.3 relative risk stems entirely from the case-control studies.<sup>23</sup> For example, Berge 2018 reported an overall relative risk of 1.22 (95% CI 1.13-1.30), but stratified its results to report relative risks of 1.26 and 1.02 (non-statistically significant) for case-control and cohort studies, respectively.<sup>24</sup> Similarly, Penninkilampi 2018 reported an overall odds ratio of 1.31, but its stratified results showed an odds ratio of 1.35 for case-control studies and a non-statistically significant odds ratio of 1.06 (95% CI 0.90-1.25) for cohort studies.<sup>25</sup>

Moreover, the meta-analyses, pooled studies and systematic reviews have consistently and repeatedly acknowledged that the available evidence does not establish causation. For example, a 2008 meta-analysis co-authored by plaintiffs’

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<sup>22</sup> See *RMSE* at 289.

<sup>23</sup> See Goodman, *Quantitative Recall Bias Analysis of the Talc and Ovarian Cancer Association*, 7 *Glob. Epidemiol.* 1, 1 (2024) (“Goodman 2024”) (Ex. 24 to Davidson Decl.) (“Meta-analyses of these studies” are “driven by the case-control studies’ results.”).

<sup>24</sup> Berge, *Genital Use of Talc and Risk of Ovarian Cancer: A Meta-analysis*, 27(3) *Eur. J. Cancer Prev.* 248, 251 (2018) (“Berge 2018”) (Ex. 25 to Davidson Decl.).

<sup>25</sup> Penninkilampi 2018 at 44.

expert Dr. Siemiatycki concluded: “The current body of experimental and epidemiological evidence is insufficient to establish a causal association between perineal use of talc and ovarian cancer risk.”<sup>26</sup> The other meta-analyses relied upon by plaintiffs’ experts similarly concluded that “a certain causal link between talc use and ovarian cancer has not yet been established,”<sup>27</sup> and that the available evidence did “not support a causal interpretation of the association.”<sup>28</sup>

A number of studies have noted that the weak association reported in many of the case-control studies (but no cohort studies) could be explained entirely by limitations inherent in the case-control study design. Recall bias (i.e., cases and controls remembering past exposures differently, even if the usage rate between the groups is the same) is especially problematic when studying talc use because it is difficult for study subjects to accurately report the extent of their use.<sup>29</sup>

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<sup>26</sup> Langseth, *Perineal Use of Talc and Risk of Ovarian Cancer*, 62 J. Epidemiol. Community Health 358, 359 (2008) (“Langseth 2008”) (Ex. 26 to Davidson Decl.).

<sup>27</sup> Penninkilampi 2018 at 42.

<sup>28</sup> Berge 2018 at 256.

<sup>29</sup> Peres, *Racial/Ethnic Differences in the Epidemiology of Ovarian Cancer: A Pooled Analysis of 12 Case-Control Studies*, 47(2) Int’l J. Epidemiol. 460, 469 (2017) (“Peres 2017”) (Ex. 27 to Davidson Decl.); *see also* Terry, *Genital Powder Use and Risk of Ovarian Cancer: A Pooled Analysis of 8,525 Cases and 9,859 Controls*, 6(8) Cancer Prev. Res. 811, 811 (2013) (“Terry 2013”) (Ex. 28 to Davidson Decl.) (“Whether risk increases with number of genital powder applications and for all histologic types of ovarian cancer also remains uncertain. . . . Among genital powder users, we observed no significant trend . . . in  
(cont’d)

The recall-bias problem associated with case-control studies has been exacerbated by media coverage of talcum powder litigation. For example, the Schildkraut 2016 study co-authored by plaintiffs' experts Drs. Cote and Moorman sought to evaluate "[t]he possibility of differential misclassification" (in other words, recall bias) "due to heightened awareness of" talc-ovarian cancer litigation that resulted from media reports in 2014.<sup>30</sup> The Schildkraut 2016 study found that women interviewed after 2014 (when talc lawsuits began receiving more significant media attention) reported a 15% higher rate of talc use, resulting in a relative risk **2.5 times higher** than the non-statistically significant relative risk reported for women interviewed before 2014.<sup>31</sup> As Dr. Cote conceded, Schildkraut 2016 "definitely [showed] an attenuation of the odds ratio [from interviews prior to 2014 and after 2014]" and presented "evidence that there was potentially recall bias in the group that was interviewed after 2014."<sup>32</sup>

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risk with increasing number of lifetime applications . . .").

<sup>30</sup> Schildkraut, *Association between Body Powder Use and Ovarian Cancer: The African American Cancer Epidemiology Study (AACES)*, 25(10) Cancer Epidemiol. Biomarkers Prev. 1411, 1416 (2016) ("Schildkraut 2016") (Ex. 29 to Davidson Decl.).

<sup>31</sup> Schildkraut 2016 at 1414 tbl. 2 (reporting, for post-2014 and pre-2014 interviewees, respectively, 51.5% versus 36.5% talc use and relative risks of 2.91 (95% CI 1.70-4.97) versus 1.19 (95% CI 0.87-1.63)).

<sup>32</sup> (3/21/24 Cote Dep. 39:5-11; *id.* 40:7-10; *id.* 277:9-18.)

Confounding (i.e., study participants having risk factors for ovarian cancer other than talc that might confuse the relationship) is also a potential explanation for the weak association between talc use and ovarian cancer in some case-control studies. For example, studies have observed that talc users are more likely than nonusers to have a number of risk-increasing characteristics, such as a high BMI, a history of smoking or alcohol use,<sup>33</sup> but many studies did not control for these characteristics. Moreover, the 2016 Gonzalez study suggests that douching—*not talc use*—might account for the association observed in case-control studies. Specifically, that study found that talc users are more likely to douche than the general population, and that douching nearly doubled the risk of ovarian cancer.<sup>34</sup> This is a significant finding because only a couple of case-control studies have adjusted for douching.

***Nature Of Ovarian Cancer.*** Ovarian cancer is not a single distinct disease; rather, there are many different subtypes of ovarian cancer.<sup>35</sup> This is significant for

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<sup>33</sup> Houghton 2014 at 3; *see also* Rosenblatt, *Characteristics of Women Who Use Perineal Powders*, 92(5) *Obstet. Gynecol.* 753, 754 (1998) (“Rosenblatt 1998”) (Ex. 30 to Davidson Decl.) (“A relatively higher proportion of women who used [talcum] powder . . . also had douched . . . , consumed alcohol . . . , or smoked cigarettes. Women in the highest BMI were relatively more likely ever to have used powder in the perineal area.”).

<sup>34</sup> Gonzalez 2016 at 799, 800-02.

<sup>35</sup> *See* Wentzensen & O’Brien 2021 at 202 (“Ovarian cancer is characterized by profound heterogeneity that can be observed in site of origin, genetic

(cont’d)

the causation question because the studies that have reported on relative risks by ovarian cancer subtype have overwhelmingly found no association between perineal talc exposure and clear cell carcinoma. For example, several meta-analyses (on which Dr. Wolf relies heavily for her general causation opinion) have reported on the association between talc use and clear cell carcinoma, with results that are all essentially equal to a null association or below it.<sup>36</sup> Indeed, of all the epidemiological studies that have analyzed the purported association between talc use and clear cell carcinoma of the ovary, only *one*, Terry 2013, shows a statistically significant increased risk (and later data in Cramer 2016 nullified that association).

***The Court's ruling.*** In April 2020, the MDL Court largely denied defendants' motion to exclude the original opinions of three of plaintiffs' experts: Drs. Carson, Clarke-Pearson and McTiernan.<sup>37</sup> The gist of Judge Wolfson's ruling

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susceptibility, somatic mutations, molecular pathways, risk factor associations and morphologic differences.”).

<sup>36</sup> See Berge 2018 at 251 (“No significant associations were detected for . . . clear cell (RR: 0.98; 95% CI: 0.72-1.23) carcinomas.”); Taher, *Critical Review of the Association Between Perineal Use of Talc Powder and Risk of Ovarian Cancer*, 90 Reproductive Toxicol. 88, 93 (2019) (“Taher 2019”) (Ex. 31 to Davidson Decl.) (OR: 0.63; 95% CI: 0.15-2.65 for “clear cell”); Penninkilampi 2018 at 44 (OR: 1.02; 95% CI: 0.75-1.39 for clear cell carcinoma; “[w]e found an increased risk of serous and endometrioid, but not mucinous or clear cell subtypes”).

<sup>37</sup> Although the J&J defendants sought to exclude the general causation

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was that the reliability of these experts' opinions (and, in particular, their application of the "Bradford Hill" methodology) was a matter of their "weight." *See, e.g., In re Johnson & Johnson*, 509 F. Supp. 3d at 148. In particular, the Court reasoned that "[t]he question of whether the relative risk found by [p]laintiffs' experts can be categorized as 'strong' or 'weak' is best left to the jury." *Id.* at 164. The Court also determined that the experts' elevation of the case-control studies over the cohort studies "relate[s] to the weight of their testimony, not their reliability." *Id.* at 172. And the Court reasoned that "while the body of evidence with respect to dose-response is inconclusive," plaintiffs' experts "explained the bases for their findings," and "it is not the Court's position as gatekeeper to determine [if their] interpretation of the studies is correct." *Id.* at 180. Although the Court found these opinions admissible, it expressly acknowledged that "studies continue to be conducted by the scientific community" and did not "foreclose the possibility" of revisiting the arguments raised by the parties in light of new data. *Id.* at 129 n.6.

### **C. New Scientific Developments Since The Court's Ruling**

O'Brien 2020—the largest pooled study of the cohort data ever performed

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opinions of Drs. Arch Carson, Daniel Clarke-Pearson, Sarah Kane, Anne McTiernan, Patricia Moorman, Jack Siemiatycki, Sonal Singh, Ellen Blair Smith, Rebecca Smith-Bindman, Judith Wolf and (in part) Laura Plunkett, the MDL Court's *Daubert* opinion only addressed the opinions offered by experts who testified live at the *Daubert* hearing: Drs. Carson, Clarke-Pearson and McTiernan.

on the issue—found “no statistically significant association between . . . use of [talcum] powder in the genital area and risk of ovarian cancer.”<sup>38</sup> The estimated HR for long-term use vs never use was 1.01 (95% CI, 0.82-1.25), with a non-statistically significant estimated HR of 1.09 (95% CI, 0.97-1.23) for frequent vs never users.<sup>39</sup> The study also found “no clear dose-response trends for duration and frequency of powder use in the genital area in relation to ovarian cancer risk.”<sup>40</sup> The main analysis included 2,168 ovarian cancer cases that developed over 3.8 million person-years, which “far exceeds” the number addressed in the earlier Penninkilampi meta-analysis.<sup>41</sup> As plaintiffs’ own experts, Dr. Siemiatycki and Dr. Wolf, agreed, O’Brien 2020 represents the “most up-to-date representation of the four cohort studies that have been conducted.”<sup>42</sup>

Following the O’Brien 2020 pooled analysis, an article was published in the

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<sup>38</sup> O’Brien, *Association of Powder Use in the Genital Area with Risk of Ovarian Cancer*, 323(1) JAMA 49, 56 (2020) (“O’Brien 2020”) (Ex. 32 to Davidson Decl.). Although O’Brien 2020 was published before the MDL Court issued its ruling, it was not part of the experts’ prior opinions and was not addressed in the *Daubert* ruling.

<sup>39</sup> *Id.*

<sup>40</sup> *Id.*

<sup>41</sup> *Id.*

<sup>42</sup> (Dep. of Jack Siemiatycki (“9/21/21 Siemiatycki Dep.”) 122:17-22, Sept. 21, 2021 (Ex. 33 to Davidson Decl.); Dep. of Judith K. Wolf (“9/13/21 Wolf Dep.”) 172:18-25, Sept. 13, 2021 (Ex. 34 to Davidson Decl.) (“I agree that [O’Brien 2020] provides the most up-to-date information of the pooled analysis of the cohort studies.”).)

journal *Gynecologic Oncology* written by the lead authors of the O'Brien paper, strongly rejecting the hypothesized link between talc use and ovarian cancer based on the totality of the evidence. The scientists concluded that "[g]iven the inability to attribute a clear causal factor to the observed associations, the lack of a good experimental model, the lack of a specific biomarker for powder-related carcinogenesis, and the inability to rule out confounding by indication, ***it is difficult to conclude that the observed associations are causal.*** Furthermore, given the widespread use of powders and the rarity of ovarian cancer, the case for public health relevance is limited."<sup>43</sup>

Recent studies also highlight that the findings of plaintiffs' touted data are skewed by bias or confounding. For example:

- O'Brien 2023 confirmed that recall bias is "potentially driving some of the previously observed differences in effect estimates between studies collecting genital powder exposure status retrospectively versus prospectively."<sup>44</sup>
- The Goodman 2024 quantitative bias assessment similarly "demonstrates that recall bias alone may have a large impact on risk estimates" in case-control studies and "that recall bias results in a bias away from the null" (i.e., away from a finding of no association).<sup>45</sup> For this reason, the Goodman 2024 authors acknowledged that "[r]ecall bias should always be assessed when there is a discrepancy

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<sup>43</sup> Wentzensen & O'Brien 2021 at 207 (emphasis added).

<sup>44</sup> O'Brien, *Douching and Genital Talc Use: Patterns of Use and Reliability of Self-Reported Exposure*, 34(3) *Epidemiology* 376, 378, 383 (2023) ("O'Brien 2023") (Ex. 35 to Davidson Decl.).

<sup>45</sup> Goodman 2024 at 3.

between case-control study results and results in cohort and animal studies when integrating these streams of evidence for causal evaluations.”<sup>46</sup>

- Davis 2021—a study co-authored by plaintiffs’ expert, Dr. Moorman—found that “[w]hen the time period was limited to women who were interviewed prior to 2014 (i.e., before ongoing lawsuits about genital powder use which had extensive media coverage), the results were attenuated and no[t] significant.” According to the authors, this “highlight[s] the potential for recall bias in case-control studies.”<sup>47</sup>

Recent studies (e.g., Chang 2024) also demonstrate that confounding may explain any positive associations reported in case-control studies. In that study, the authors noted that within the hygiene product category, the *only* product significantly associated with ovarian cancer was douche,<sup>48</sup> suggesting that if there is an increased risk of ovarian cancer from personal care products, *the association is with douching*, which most studies did not account for.

Plaintiffs’ experts claim that some of the newly published literature supports their conclusions; it does not. For one thing, much of it was published by paid plaintiffs’ experts in this litigation, and many of those papers have been criticized. For example, the National Cancer Institute (“NCI”) has discredited Woolen 2022

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<sup>46</sup> *Id.*

<sup>47</sup> Davis, *Genital Powder Use and Risk of Epithelial Ovarian Cancer in the Ovarian Cancer in Women of African Ancestry Consortium*, 30(9) Cancer Epidemiol. Biomarkers Prev. 1660 (2021) (“Davis 2021”) (Ex. 36 to Davidson Decl.)

<sup>48</sup> See Chang 2024 at 5.

(a study co-authored by Dr. Smith-Bindman), stating that “because of the structure of [Woolen 2022’s] analysis, *the results should be interpreted with care.*”<sup>49</sup> And the papers authored by now-withdrawn former expert Dr. Ghassan Saed were rejected by multiple journals, including one that referred to his work as “outrageous,” as discussed more fully in Defendants’ Biological Plausibility *Daubert* Brief.

O’Brien 2024—which relied, in part, on retrospective questionnaires and imputed data—does not support plaintiffs’ theories of general causation either. The authors of that study sought to rely on retrospective surveys to obtain more information on talc use from women in the Sister Study, but many respondents either provided contradictory responses or failed to respond to the follow-up survey. In an effort to address the significant amount of missing data, the paper modeled various scenarios using data that were largely “imputed”—i.e., made up. While plaintiffs’ experts tout this study as “a new and innovative analysis of data,”<sup>50</sup> it is, at bottom, guesswork; presumably for that reason, the authors cautioned that the “*results do not establish causality and do not implicate any specific cancer-inducing agent.*”<sup>51</sup>

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<sup>49</sup> NCI 2024 PDQ (emphasis added).

<sup>50</sup> (Siemiatycki 3d Am. Rep. at 53.)

<sup>51</sup> O’Brien 2024 at 13 (emphasis added); *see also id.* at 14 (“[O]ur findings . . . do not pinpoint a specific cause of mechanism . . .”).

Importantly, when the O'Brien authors looked at actual prospective data, there was no association between talc and ovarian cancer (HR: 1.02, 95% CI: 0.79-1.34). Thus, the purported association was driven entirely by the imputed results, not real ones. The disparity in results between actual and imputed data are particularly concerning because, in constructing their imputed results, the authors made a series of choices that systematically overestimated levels of talc use for women with missing data, a group that included a disproportionate number of cancer cases. First, the authors "corrected" results by assuming exposure for the vast majority of women who provided contradictory answers prospectively at enrollment and retrospectively follow-up. Still the association remained non-significant.<sup>52</sup> Only after also adding a complex imputation model to guess how women who failed to respond to the follow-up survey would have responded did the authors show a significant association.<sup>53</sup> Critically, the imputation model was applied to women who had reported no talc use in the prospective survey;<sup>54</sup> in other words, every woman who was classified as a talc user under the imputations had originally reported no talc exposure.

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<sup>52</sup> *Id.* at Table 2, Scenario 2; Table A5, Scenario 2.

<sup>53</sup> Table 2, Scenario 4; Table A5, Scenario 4.

<sup>54</sup> Women who initially reported talc exposure and failed to respond to follow-up were coded as exposed.

***Recent public health pronouncements.*** Numerous U.S. regulatory and medical bodies have reiterated their rejection of plaintiffs' proffered causal theory. For example:

- The Centers for Disease Control and Prevention's ("CDC") website was updated in October 2023 and does not list talc use as a risk factor for ovarian cancer.<sup>55</sup>
- The American College of Obstetricians and Gynecologists ("ACOG") similarly updated its frequently asked questions on ovarian cancer in May 2022 and does not list talc as a risk factor for ovarian cancer.<sup>56</sup> This is consistent with the organization's prior statement that "[t]here is no medical consensus that talcum powder causes ovarian cancer."<sup>57</sup> It also aligns with ACOG's Committee Opinion #619, recommending talc application as a modality to reduce postoperative wound complications in obese patients.<sup>58</sup>
- The Society of Gynecologic Oncology identifies established risk factors for ovarian cancer on its website and does not list talc.<sup>59</sup>
- In 2023, the CDC funded ACOG to form an expert review panel that included members from a number of national societies, including, among others, the American Cancer Society, American Society of

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<sup>55</sup> <https://www.cdc.gov/ovarian-cancer/risk-factors/index.html>.

<sup>56</sup> <https://www.acog.org/womens-health/faqs/ovarian-cancer>.

<sup>57</sup> Talc Use and Ovarian Cancer, American College of Obstetricians and Gynecologists (Sept. 11, 2017), <https://www.acog.org/news/news-releases/2017/09/talc-use-and-ovarian-cancer>.

<sup>58</sup> Committee Opinion No. 619: Gynecologic Surgery in the Obese Woman, American College of Obstetricians and Gynecologists (Jan. 2015, reaffirmed 2019), <https://www.acog.org/-/media/project/acog/acogorg/clinical/files/committee-opinion/articles/2015/01/gynecologic-surgery-in-the-obese-woman.pdf>.

<sup>59</sup> Ovarian Cancer Risk Factors, Society of Gynecologic Oncology, <https://www.sgo.org/patients-caregivers-survivors/caregivers/ovarian-cancer-risk-factors/> (last visited July 2, 2024).

Clinical Oncology, the National Comprehensive Cancer Network (“NCCN”), and others.<sup>60</sup> This group reviewed the literature and identified “research gaps” in every area of ovarian cancer research, including risk factors. Talc was not mentioned in any of the research gaps. Their review found “heterogeneity in the studies on the use of talcum powder and ovarian cancer risk.”<sup>61</sup>

- The NCCN found that “[e]nvironmental factors have been investigated, such as talc, but so far they have not been conclusively associated with the development of this neoplasm.”<sup>62</sup>
- The National Cancer Institute PDQ, which was updated in March 2024, states that “the data are inadequate to support an association between perineal talc exposure and an increased risk of ovarian cancer.”<sup>63</sup>
- The American Cancer Society concluded this year that “[t]he weight of the evidence does not support an association between ovarian cancer and genital exposure to talc-based powder.”<sup>64</sup>
- All of these recent public statements mirror the views of the FDA, which “did not find that the data submitted presented conclusive evidence of a causal association between talc use in the perineal area

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<sup>60</sup> Burke, *Executive Summary of the Ovarian Cancer Evidence Review Conference*, 142(1) *Obstet. Gynecol.* 179, 191 (2023) (Ex. 37 to Davidson Decl.).

<sup>61</sup> *Id.* at 183.

<sup>62</sup> Clinical Practice Guidelines in Oncology: Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer, National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, <https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1453>.

<sup>63</sup> NCI 2024 PDQ.

<sup>64</sup> Cancer Facts & Figures 2024, at 23, American Cancer Society, <https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2024/2024-cancer-facts-and-figures-acf.pdf>.

and ovarian cancer.”<sup>65</sup>

While IARC recently reclassified talc as “probably carcinogenic to humans,” it made clear that “a causal role for talc could **not** be fully established” in light of “biases in how talc use was reported in the epidemiological studies.”<sup>66</sup> As a member of the IARC working group explained, because “[s]elf-reporting can sometimes be unreliable . . . the human study evidence was **not** strong enough to say that talc causes ovarian cancer.”<sup>67</sup>

**D. Plaintiffs’ Experts’ Unreliable Opinions.**

As previously noted, the Court’s prior ruling only addressed the original opinions of Drs. McTiernan, Clarke-Pearson and Carson. Although Dr. McTiernan—an epidemiologist and frequent testifier in talcum powder litigation—continues to opine that the cohort study results should be disregarded because they did not contain enough ovarian cancer endpoints and therefore lack sufficient statistical power,<sup>68</sup> “the largest study of [talc and ovarian cancer] to date”<sup>69</sup> now demonstrates that Dr. McTiernan’s “power” argument has no scientific basis. Dr.

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<sup>65</sup> FDA Denial Letter at 1.

<sup>66</sup> IARC Press Release (emphasis added).

<sup>67</sup> O’Brien Statement (emphasis added); *see also* Stayner 2024 at 2 (IARC’s reclassification is based on “**limited**” evidence that talc causes ovarian cancer in humans”) (emphasis added).

<sup>68</sup> (McTiernan 3d Am. Rep. at 61-62.)

<sup>69</sup> O’Brien 2020 at 56.

McTiernan does not meaningfully account for this new scientific development, and she fails to consider the conclusions of objective scientific literature published within the last couple of years that contradict her theory of causation.

Notably, another court recently excluded Dr. McTiernan’s causation opinions regarding Zantac for her use of “result-driven reasoning” and an unreliable methodology in assessing epidemiology. Specifically, the court criticized Dr. McTiernan’s “routine” disregard for statistical significance and “frequent reliance upon statistically insignificant data”; rejection of study authors’ cautions and conclusions; practice of “selective[ly] disregard[ing] . . . data within a study that does not tend to support her conclusion”; and disregard for the consensus of “the scientific community.” *See In re Zantac*, 644 F. Supp. 3d at 1222, 1234, 1237-39, 1242, 1254. Dr. McTiernan conceded that she “used the same methodology for [her] work on *Zantac*” as she used in her assessment of the epidemiology related to talc use and ovarian cancer.<sup>70</sup>

Dr. Clarke-Pearson is a gynecologic oncologist who describes the meta- and pooled analyses as “much stronger in that they include larger numbers of patients resulting in greater statistical power.”<sup>71</sup> Although the Court admitted his original

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<sup>70</sup> (Dep. of Anne McTiernan (“McTiernan MS AG Dep.”) 126:17-127:12, *State ex rel. Fitch v. Johnson & Johnson*, No. 25CH1:14-cv-001207 (Miss. Ch. Ct. Oct. 3, 2023) (Ex. 38 to Davidson Decl.).)

<sup>71</sup> (Clarke-Pearson 3d Am. Rep. at 2, 9.)

opinions, Dr. Clarke-Pearson fails to reconcile the recent findings of O'Brien 2020—which he concedes “concluded that there was not a statistically significant association between the genital use of powder and an increased risk of ovarian cancer”—with his opinion that these studies demonstrated “a consistent and statistically significant increased risk of developing EOC with perineal talcum powder use.”<sup>72</sup> Nor does he meaningfully consider the impact of recall bias and confounding on the risk estimates.<sup>73</sup>

Plaintiffs' experts who were not addressed in the prior ruling employ a similar approach to the scientific literature. For example, Dr. Cote broadly contends that “biases . . . did not invalidate the associations seen” in case-control studies because perineal talc use “is unlikely to be a sensitive subject.”<sup>74</sup> But contrary to this conclusion, she admits that her prior publication (Schildkraut 2016) “definitely [showed] an attenuation of the odds ratio [from interviews prior to 2014

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<sup>72</sup> (*Id.* at 9-10.)

<sup>73</sup> Dr. Carson is a toxicologist who opined in 2018 that based on his consideration of the Bradford Hill factors and “a risk assessment,” there is a “cause and effect relationship between the use of talc” and ovarian cancer. (Rep. of Arch Carson (“Carson Rep.”) at 10-11, Nov. 16, 2018 (Ex. 39 to Davidson Decl.).) Although the Court admitted Dr. Carson’s general causation opinions, Dr. Carson failed to provide an updated report or testimony to address any of the recent objective scientific literature that undermines and discredits the methodology Dr. Carson utilized to reach his general causation opinion. Accordingly, Dr. Carson’s opinions are outdated.

<sup>74</sup> (Cote Am. Rep. at 29, 39.)

and after 2014]” and presented “evidence that there was potentially recall bias in the group that was interviewed after 2014.”<sup>75</sup> Dr. Harlow similarly concludes that recent meta-analyses demonstrate “a consistent association between frequent talc use and ovarian cancer,” and that it is “not plausible that recall bias can explain away the association.”<sup>76</sup> However, Dr. Harlow’s own prior published work concluded that “the perineal application of baby powder . . . was [not] associated with an appreciably altered risk of borderline ovarian tumors”<sup>77</sup>; “no significant dose response was observed between total genital talc applications of talc and ovarian cancer risk”<sup>78</sup>; and “[r]ecall bias is possible because talc exposure in these studies is based on personal recollection.”<sup>79</sup>

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<sup>75</sup> (3/21/24 Cote Dep. 39:5-11, 40:7-10, 277:9-18.) *See also* Schildkraut 2016 at 1414 tbl. 2.

<sup>76</sup> (Harlow Rep. at 6.)

<sup>77</sup> Harlow & Weiss, *A Case-Control Study of Borderline Ovarian Tumors: the Influence of Perineal Exposure to Talc*, 130(2) Am. J. Epidemiol. 390, 390 (1989) (“Harlow & Weiss 1989”) (Ex. 40 to Davidson Decl.).

<sup>78</sup> *Id.* at 25.

<sup>79</sup> Cramer, *Genital Talc Exposure and Risk of Ovarian Cancer*, 81(3) Int’l J. Cancer 351, 354 (1999) (“Cramer 1999”) (Ex. 41 to Davidson Decl.). Dr. Kenneth Rothman co-authored Dr. Harlow’s expert report, and prior to doing so, published that “the results from epidemiologic studies to date measuring the relation between talc and ovarian cancer risk gives an overall relative risk of 1.31,” which are “weak positive association[s]” that can be “easily explain[ed]” by “[b]ias” or “[u]ncontrolled confounding,” and thus, the evidence “does not indicate that talc can be ‘reasonably anticipated to be a human carcinogen.’” Rothman, *Interpretation of Epidemiologic Studies on Talc and Ovarian Cancer*, at 1, Nov. 28, 2000 (“Rothman 2000”) (Ex. 42 to Davidson Decl.).

Dr. Moorman states that Davis 2021 reported an “increased risk of ovarian cancer,” which “strengthen[s] [her] opinion that genital talc use is a cause of ovarian cancer.”<sup>80</sup> But Dr. Moorman left out important findings from her own study, including that: (1) “[t]here was not a dose-response relationship regarding frequency or duration of genital powder use and ovarian cancer”; and (2) “[w]hen the time period was limited to women who were interviewed prior to 2014 (i.e., before ongoing lawsuits about genital powder use which had extensive media coverage), the results were attenuated and no[t] . . . significant,” which “highlight[s] the potential for recall bias in case-control studies.”<sup>81</sup>

The *Zantac* court recently excluded Dr. Moorman’s unreliable and “conclusion-oriented process” in assessing epidemiology, noting that Dr. Moorman erred in the following ways: (1) she “omit[ted] and all but ignore[d] the study authors’ conclusions in the studies she relies upon, the majority of which contradict her opinion”; (2) her general causation conclusions “are unique and isolated to this litigation—no independent scientist or publication has concluded that ranitidine causes cancer”; and (3) she failed to “address epidemiologic evidence that is

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<sup>80</sup> (Suppl. Rep. of Patricia G. Moorman (“Moorman Suppl. Rep.”) at 2, 8, 11, Nov. 15, 2023 (Ex. 43 to Davidson Decl.).)

<sup>81</sup> Davis 2021 at 1661, 1663-65.

inconsistent with . . . her causation opinions.” *In re Zantac*, 644 F. Supp. 3d at 1253-55.

Similar to Dr. Moorman, Dr. Smith-Bindman published just two years ago in Woolen 2022 that “[t]he risk of ovarian cancer in women with frequent perineal talcum powder product”—i.e., dose-response—“is not well understood.”<sup>82</sup> The Woolen 2022 article was derived from a meta-analysis that Dr. Smith-Bindman conducted as a plaintiffs’ expert in talc litigation.<sup>83</sup> Because Woolen 2022 was a post hoc analysis that used subjective and inconsistent criteria to narrow the data it examined, the NCI currently states that its “results should be interpreted with care.”<sup>84</sup>

Dr. Siemiatycki co-authored a meta-analysis in 2008, which recognized that the cohort study design is “the strongest” “because of its partly prospective ascertainment of exposure” and that “recall bias should always be considered in case-control studies.”<sup>85</sup> According to his published study, “the epidemiological evidence suggests that use of cosmetic talc in the perineal area may be associated

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<sup>82</sup> Woolen, *Association Between the Frequent Use of Perineal Talcum Powder Products and Ovarian Cancer: a Systematic Review and Meta-analysis*, 37(10) J. Gen. Intern. Med. 2526, 2526 (2022) (“Woolen 2022”) (Ex. 44 to Davidson Decl.) (emphasis added).

<sup>83</sup> (E.g., 3/20/24 Smith-Bindman Dep. 20:9-14.)

<sup>84</sup> NCI 2024 PDQ.

<sup>85</sup> Langseth 2008 at 358.

with ovarian cancer risk,” but “the absence of clear exposure-response associations in most studies, as well as the absence of an overall excess risk in the cohort study” undermined the association findings.<sup>86</sup> As a plaintiffs’ expert, Dr. Siemiatycki now seeks to opine that the “meta-analyses show[] that there is incontrovertible evidence that there is a strong association” between talc and ovarian cancer,<sup>87</sup> and disregards the impact of recall bias on those studies.<sup>88</sup>

Dr. Singh opines that “[a] high percentage . . . of the epidemiologic studies examined have ORs” greater than 1.<sup>89</sup> But as another court recognized in excluding Dr. Singh’s general causation opinion, “Dr. Singh’s reliance on non-statistically significant ‘trends’ is [not] accepted in [the] field” and has not “served as the basis for any epidemiologist’s causation opinion in peer-reviewed literature.” *In re Lipitor (Atorvastatin Calcium) Mktg., Sales Pracs. & Prods. Liab. Litig.*, 892 F.3d 624, 641-42 (4th Cir. 2018) (citation omitted).

### **LEGAL STANDARD**

Under recently amended Fed. R. Evid. 702, plaintiffs must “demonstrate[] to the [C]ourt that it is more likely than not” that their experts are sufficiently qualified; that their opinions are “based on sufficient facts or data”; that the

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<sup>86</sup> *Id.* at 359.

<sup>87</sup> (3/27/24 Siemiatycki Dep. 226:22-24.)

<sup>88</sup> (*E.g.*, Siemiatycki 3d Am. Rep. at 63, 67-68.)

<sup>89</sup> (*Id.* at 20.)

opinions are the “product of reliable principles and methods”; and that they reflect a “reliable application of the principles and methods to the facts of the case.” Fed. R. Evid. 702. “[O]ne purpose of the amendment[s] was to emphasize that ‘[j]udicial gatekeeping is essential.’” *Acetaminophen I*, 2023 U.S. Dist. LEXIS 224899, at \*49 n.27 (citation omitted). In addition to clarifying that the “proponent” of expert testimony bears the burden of proving its admissibility, “Rule 702’s recent amendments were drafted to correct some court decisions incorrectly holding” that fundamental reliability challenges “are questions of weight and not admissibility.” *In re Onglyza*, 93 F.4th at 348 n.7 (quoting Fed. R. Evid. 702 advisory committee’s note to 2023 amendments).<sup>90</sup>

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<sup>90</sup> See also, e.g., *Sardis v. Overhead Door Corp.*, 10 F.4th 268, 284 (4th Cir. 2021) (the amendment clarifies that it is an “abdication of [the] gatekeeping role” to punt “critical” reliability and methodology questions to lay juries) (citation omitted); *In re Deepwater Horizon Belo Cases*, No. 19-963 et al., 2024 U.S. Dist. LEXIS 112817, at \*50-52 (N.D. Fla. June 25, 2024) (“The amendment was motivated by the Advisory Committee’s observation that in a number of federal cases . . . judges did not apply the preponderance standard of admissibility to Rule 702’s requirements of sufficiency of basis and reliable application of principles and methods, instead holding that such issues were ones of weight for the jury[,]’ which is ‘an incorrect application of Rules 702 and 104(a).’”) (citation omitted); *In re Paraquat Prods. Liab. Litig.*, MDL No. 3004, 2024 WL 1659687, at \*4 nn.8 & 9 (S.D. Ill. Apr. 17, 2024), *appeal filed* (“The Advisory Committee thus appears to have found that courts had erroneously admitted unreliable expert testimony based on the assumption that the jury would properly judge reliability . . . .”); *Johnson v. United States*, No. 21-2851, 2024 U.S. Dist. LEXIS 53513, at \*9 n.7 (E.D.N.Y. Jan. 16, 2024) (“The amendment was aimed at courts that had erroneously held that ‘the critical questions of the sufficiency of an expert’s basis, and the application of the expert’s methodology, are questions of weight and not admissibility.’”) (citation omitted).

Judge Wolfson did not have the benefit of these clarifications, which explains why significant swaths of her ruling misapprehend the pertinent legal standard. Indeed, the phrase “preponderance of the evidence” appears just three times in the ruling, each time as part of a case parenthetical. *See In re Johnson & Johnson*, 509 F. Supp. 3d at 148 (quoting *Crowley v. Chait*, 322 F. Supp. 2d 530, 537 (D.N.J. 2004)); *id.* at 187 (quoting *In re Processed Egg Prods. Antitrust Litig.*, 81 F. Supp. 3d 412, 416 (E.D. Pa. 2015)); *id.* at 164 n.37 (quoting *Pick v. Am. Med. Sys., Inc.*, 958 F. Supp. 1151, 1160 (E.D. La. 1997)). In addition, the Court held that plaintiffs’ experts’ proffered opinions on the mechanism by which talc is theorized to cause ovarian cancer were admissible because “Defendants ha[d] not introduced any evidence that this theory has been disproven as a matter of science.” *In re Johnson & Johnson*, 509 F. Supp. 3d at 175. In other words, Judge Wolfson not only failed to hold plaintiffs’ experts to the proper standard, but she essentially “reverse[d] the burden of proof.” *See In re Onglyza*, 93 F.4th at 345 (excluding opinion that the literature “should be interpreted as cause-and-effect unless there is compelling evidence to prove otherwise”) (citation omitted); *see also In re Acetaminophen II*, 2024 U.S. Dist. LEXIS 121259, at \*62. Analyzed under the proper standard, plaintiffs’ experts’ general causation opinions do not survive Rule 702 scrutiny.

## ARGUMENT

The methodology applied by plaintiffs' general causation experts is known as Bradford Hill, a list of nine factors established by Sir Austin Bradford Hill, a British mathematical statistician,<sup>91</sup> to help epidemiologists "distinguish a causal connection from a mere association." *In re Zolof*, 858 F.3d at 795. These factors are: (1) ***strength of association*** (the magnitude of the reported association); (2) ***consistency of association*** (whether different studies consistently report the association); (3) ***specificity*** (whether the variable is associated with a specific disease); (4) ***temporality*** (whether the exposure precedes disease onset); (5) ***coherence*** (whether the causal hypothesis is logical or contradicts existing knowledge); (6) ***dose-response or biological gradient*** (whether greater exposure increases risk or vice versa); (7) ***biological plausibility*** (whether there is a valid means through which an agent could cause the disease); (8) ***experimental evidence*** (whether experimental studies support the posited association); and (9) ***analogy*** (whether the association can reasonably be compared to other associations that have been accepted as causal).<sup>92</sup>

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<sup>91</sup> See generally Hill, *The Environment and Disease: Association or Causation?* 295 (1965) ("Hill 1965") (Ex. 45 to Davidson Decl.).

<sup>92</sup> *Id.* at 295-99.

As explained below, while Bradford Hill is itself a reliable methodology, the key question under Rule 702 is whether the challenged experts have applied it reliably. Although Judge Wolfson held that “it is not for the Court to decide” whether plaintiffs’ experts properly applied the Bradford Hill considerations and that doing so “would unnecessarily broaden the scope of this Court’s role as a gatekeeper,” *In re Johnson & Johnson*, 509 F. Supp. 3d at 164 (strength); *see also id.* at 171-72 (consistency), the law is now crystal clear that this is precisely what the Court is supposed to do.

As courts applying the recently amended Rule 702 have recognized, even though “Bradford Hill is undeniably a reliable methodology . . . the district court ha[s] an independent duty to ensure that all experts ‘reliably applied’ Bradford Hill.” *In re Onglyza*, 93 F.4th at 347; *accord In re Acetaminophen I*, 2023 U.S. Dist. LEXIS 224899, at \*56 (excluding experts who engaged in unreliable Bradford Hill causation analyses like those here); *In re Acetaminophen II*, 2024 U.S. Dist. LEXIS 121259, at \*48 (While “[t]he Bradford Hill analysis has been found to be a ‘generally reliable’ methodology . . . Rule 702 requires . . . that an expert not only use ‘reliable principles and methods’ but also that ‘the expert’s opinion reflects a reliable application of the principles and methods to the facts of the case.’”) (quoting Fed. R. Evid. 702). In fact, it is particularly “critical” to scrutinize an expert’s application of the Bradford Hill factors because they ““can

be implemented in multiple ways” and are therefore prone to being

“unacceptably manipulable.” *In re Acetaminophen I*, 2023 U.S. Dist. LEXIS 224899, at \*109 (citation omitted).

Plaintiffs’ experts’ Bradford Hill analyses do exactly that and therefore fail to meet the requirements of Rule 702.

**I. PLAINTIFFS’ EXPERTS MISAPPLY THE “CORNERSTONE” OF BRADFORD HILL BY PRETENDING THAT A FACIALLY WEAK ASSOCIATION IS STRONG.**

“First upon my list I would put the strength of the association.”<sup>93</sup>

“Strength of the association is the ‘cornerstone for causal inferences’ because ‘[t]he higher the relative risk, the stronger the association and the lower the chance that the effect is spurious.’” *In re Paraquat*, 2024 WL 1659687, at \*38-39 (quoting *RMSE* at 602). It is generally accepted that a relative risk under 2.0 (i.e., a doubling of the risk) is facially weak. *In re Viagra (Sildenafil Citrate) & Cialis (Tadalafil) Prods. Liab. Litig.*, 424 F. Supp. 3d 781, 796 (N.D. Cal. 2020) (“the risk factor that emerged across all the studies was somewhere around 1.2,” which “undeniably is not a strong association.”). Here, the relative risk is much lower (approximately 1.3-1.6 in the meta-analyses on which plaintiffs’ experts rely), weighing heavily against causation.<sup>94</sup> As one court recently explained,

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<sup>93</sup> Hill 1965 at 295.

<sup>94</sup> See, e.g., FDA Denial Letter at 4 (discounting the case-control studies that  
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“lower relative risks” like these must be “scrutinize[d] . . . more closely because there is a greater chance that they are the result of uncontrolled confounding or biases” and “risk ratios between 1.0 and 2.0” are small—in fact, “far smaller” than the ones “identified by [other] experts” in other cases where opinions on strength were deemed unreliable. *In re Acetaminophen I*, 2023 U.S. Dist. LEXIS 224899, at \*81-82 (quoting *RMSE* at 602). Plaintiffs’ experts nonetheless all claim that a “strong” association *has* been reported between talc use and ovarian cancer.<sup>95</sup> This alone requires exclusion of their opinions.

Several of plaintiffs’ experts argue that even though the relative risk is mathematically weak, it should be deemed significant as a matter of policy because

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found a “small positive association[]” because they have confidence intervals that “are often close to 1.0”); Micha 2022 at 931 (“[P]ositive associations derived from case-control studies have been remote and the putative causal factors remain inconclusive.”); Gossett & del Carmen, *Use of Powder in the Genital Area and Ovarian Cancer Risk: Examining the Evidence*, 323(1) JAMA 29, 29 (2020) (“Gossett 2020”) (Ex. 46 to Davidson Decl.) (“Several case-control studies identified an increased risk of ovarian cancer with relatively small effect sizes . . . .”); Wentzensen & O’Brien 2021 at 206 (referencing “the observed weak associations between genital powder use and ovarian cancer risk”).

<sup>95</sup> (Smith-Bindman 3d Am. Rep. at 35 (noting an “extremely strong” association); Rep. of Sonal Singh (“Singh Rep.”) at 17, 63, Nov. 16, 2018 (Ex. 47 to Davidson Decl.) (the “strength of association . . . is significant”); Rep. of Ellen Blair Smith (“Smith Rep.”) at 19, Nov. 16, 2018 (Ex. 48 to Davidson Decl.) (describing a “significant” association); Carson Rep. at 9-10 (“strong” and “compelling strength of association”); McTiernan 3d Am. Rep. at 96-98 (increased risk of 22-31% “strongly supports a causal association”); Siemiatycki 3d Am. Rep. at 71, 76 (asserting that “[t]he meta-[risk ratio]” of 1.30 is “high and significant”).)

it can have a “great[] impact on a number of people” considering the number of women who use talc and the grim prognosis for many ovarian cancers.<sup>96</sup> But this is a litigation argument, rather than a scientific assessment; the question in a Bradford Hill analysis is whether an exposure causes a disease—not the gravity of the disease at issue. *See In re Acetaminophen I*, 2023 U.S. Dist. LEXIS 224899, at \*105-06 (arguments regarding “the direction of the association evidence” and the fact that the FDA has supposedly not been “vigilant in reviewing the risks” “do not relieve the Court of the obligation to scrutinize” experts’ methodology).

Some of plaintiffs’ experts also point to other exposures that have been deemed to cause disease *despite* low relative risks, such as second-hand smoking

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<sup>96</sup> (Smith-Bindman 3d Am. Rep. at 34, 36 (concluding that strength of association is met because there “is a tremendous number of cases caused by a cosmetic product that provides no medical benefit”); *id.* at 35 (“a 50% risk increase is substantial and particularly important for ovarian cancer, which has a high mortality rate, with rare early detection”); McTiernan 3d Am. Rep. at 66 (opining “for agents like perineal talcum powder products that have such a high prevalence of use . . . the odds ratio/relative risk/hazard ratio for perineal talc use is of great importance for . . . public health”); *id.* at 97 (“given the high prevalence of use of talcum powder products in this population, these levels of risk present a clinically significant public health concern,” which supports the strength factor); Clarke-Pearson 3d Am. Rep. at 13 (opining strength is “critically important” given “the severity and frequency of ovarian cancer and the preventable nature of talcum powder usage”); Moorman Rep. at 14; Smith Rep. at 19; Cote Am. Rep. at 6, 36; Wolf 3d Am. Rep. at 19 (all similar); Dep. of Michele L. Cote (“3/21/24 Cote Dep.”) 185:19-186:25, Mar. 21, 2024 (Ex. 49 to Davidson Decl.) (“Any increase in risk, whether it is small -- with respect to a product that does not have any sort of medicinal benefit, that it is not small.”).)

and lung cancer, or hormone therapy and breast cancer.<sup>97</sup> But the fact that some low elevations in risk have been regarded as causal in circumstances where other Bradford Hill factors—such as dose-response, consistency and biological plausibility—were particularly compelling does not mean that low observed associations can be described as strong.

The proffered associations plaintiffs’ experts discuss in their strength analysis do not suggest otherwise. With respect to secondhand smoke and cancer, for example, there was evidence of an obvious causal mechanism, clear support by analogy to smoking and cancer, and more than 50 consistent epidemiological studies from more than 20 countries, all of which are missing here.<sup>98</sup> And the

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<sup>97</sup> (Moorman Rep. at 12-13 (discussing “some other well-accepted exposure-disease associations that have relative risks of similar magnitude and are generally accepted to be causal”); Siemiatycki 3d Am. Rep. at 71 (identifying other exposures that he opines have similar risk ratios and are “well-recognized risk factors for cancer and other diseases”); Suppl. Rep. of Sonal Singh (“Singh Suppl. Rep.”) at 19, Nov. 15, 2023 (Ex. 50 to Davidson Decl.) (“There are several noteworthy examples of well-established causal relationships where the strength of the association is in the order of 20-40%.”); Rep. of Sarah E. Kane (“Kane Rep.”) at 33, Nov. 15, 2018 (Ex. 51 to Davidson Decl.) (“There are a number of examples of causal relationships where the relative risk is less than 2.0 (e.g., second hand smoke and lung cancer, oral contraceptive use and breast cancer, radon exposure and lung cancer).”); Harlow Rep. at 4 (“[M]any associations known to be causal, such as the association between cigarette smoking and cardiovascular disease, are weak.”); McTiernan 3d Am. Rep. at 10, 29-31, 66 (“There are many instances in which relative risks less than 1.5 are widely accepted within the scientific community as being causative . . . .”).)

<sup>98</sup> U.S. Department of Health and Human Services. *The Health Consequences of Smoking: A Report of the Surgeon General*, Atlanta, GA: U.S. Department of  
(cont’d)

association between hormone therapy drugs and breast cancer was demonstrated by controlled clinical trials (which avoid the risks of bias and confounding).<sup>99</sup>

Here, by contrast, the remaining Bradford Hill factors are not satisfied and the low associations are particularly concerning because there are strong indications that the data are affected by both recall bias and confounding. While the Court previously ruled that plaintiffs' experts' treatment of these concepts were "inquiries" for "cross-examination," *In re Johnson & Johnson*, 509 F. Supp. 3d at 550, their distorted approach to these important scientific concepts implicates admissibility, not the weight of their testimony. *See In re Acetaminophen I*, 2023 U.S. Dist. LEXIS 224899, at \*93-94 ("[F]ailure to assess with sufficient rigor the relevant evidence of confounding by genetics . . . [b]y itself . . . requires the exclusion of his opinion.").

**Recall bias.** As explained above, recall bias is a form of information bias caused by the fact that "individuals with diseases (cases) tend to recall past exposures more readily than individuals with no disease (controls)," which artificially inflates the observed association in retrospective studies. *RMSE* at 586.

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Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health (2004), [https://www.ncbi.nlm.nih.gov/books/NBK44695/pdf/Bookshelf\\_NBK44695.pdf](https://www.ncbi.nlm.nih.gov/books/NBK44695/pdf/Bookshelf_NBK44695.pdf).

<sup>99</sup> (McTiernan 3d Am. Rep. at 30.)

Several studies examining the potential relationship between cosmetic talc exposure and ovarian cancer have conclusively demonstrated the presence of recall bias. Because recall bias affects only studies in which “the researcher is required to interview the subjects about past exposures,” *id.*, it can explain the divergence between the results of prospective cohort studies and retrospective case-control studies. As noted above:

- O’Brien 2023 “collected retrospective data on douching and genital talc use” and evaluated the reliability and consistency of self-reported exposure data used in observational studies. The authors reported that most women were more likely to report talc use at enrollment than at follow up. But among those with intervening ovarian cancer diagnoses the situation was reversed, 28% of participants self-reported genital talc use at study enrollment compared to 33% of participants self-reported genital talc use in the post-diagnosis follow-up questionnaire. These data thus provide evidence of recall bias that “potentially [is] driving some of the previously observed differences in effect estimates between studies collecting genital powder exposure status retrospectively versus prospectively.”<sup>100</sup>
- Goodman 2024 similarly “demonstrates that recall bias alone may have a large impact on risk estimates” in case-control studies and “that recall bias results in a bias away from the null” (i.e., results in studies reporting an association that does not really exist).<sup>101</sup> Specifically, when adjusting the reported findings in Cramer 2016 (a case-control study touted by plaintiffs’ experts) for several plausible recall bias models, the results were no longer statistically significant (except in one model, which reported a significant *protective* effect).<sup>102</sup>

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<sup>100</sup> O’Brien 2023 at 376, 378, 383.

<sup>101</sup> Goodman 2024 at 3.

<sup>102</sup> *Id.* at 2 tbl. 1.

- Schildkraut 2016 surveyed women both before and after widespread publicity surrounding talc litigation. It found that women interviewed after 2014 (when talc lawsuits began receiving more significant media attention) were 15% more likely to report talc use. The statistical effect was remarkable. Among pre-2014 respondents, there was no statistically significant association between talc and cancer (OR 1.26, 95% CI: 0.69-2.32). Among post-2014 respondents, the risk was not just significant but among the highest reported in talc studies (OR 2.91, 95% CI: 1.70-4.97).<sup>103</sup> As Dr. Cote, a co-author of this study, conceded, Schildkraut 2016 “definitely [showed] an attenuation of the odds ratio [from interviews prior to 2014 and after 2014]” and presented “evidence that there was potentially recall bias in the group that was interviewed after 2014.”<sup>104</sup>
- A recent study co-authored by plaintiffs’ expert Dr. Moorman echoed the findings of Schildkraut 2016 that “[w]hen the time period was limited to women who were interviewed prior to 2014 (i.e., before ongoing lawsuits about genital powder use which had extensive media coverage), the results were attenuated and no[t] significant.”<sup>105</sup> For this reason, the Davis authors only included data from individuals interviewed prior to 2014 “to avoid possible reporting bias resulting from lawsuits.”<sup>106</sup> While the authors still reported a (weak) association, they acknowledged that recall bias remained a concern for data collected before 2014 too.

Dr. Moorman’s study “highlight[s] the potential for recall bias in case-control studies”<sup>107</sup> and illustrates why she and the other experts cannot simply

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<sup>103</sup> Schildkraut 2016 at 1414 tbl. 2 (reporting, for post-2014 and pre-2014 interviewees, respectively, 51.5% versus 36.5% talc use and relative risks of 2.91 (95% CI 1.70-4.97) versus 1.19 (95% CI 0.87-1.63)).

<sup>104</sup> (3/21/24 Cote Dep. 39:5-11; *id.* 40:7-10; *id.* 277:9-18.)

<sup>105</sup> Davis 2021 at 1664-65.

<sup>106</sup> *Id.* at 1665-66.

<sup>107</sup> *Id.*

acknowledge this significant weakness of their cited literature; rather, they must “grapple” with it and “explain why [their] conclusion is scientifically justified” in the face of that contrary evidence. *In re Paraquat*, 2024 WL 1659687, at \*37. They have not.

At most, some of these experts twist the findings of another recent study (O’Brien 2024) as “prov[ing] that recall bias does not explain the relative risks.”<sup>108</sup> But O’Brien 2024 expressly recognized that “concerns about recall bias . . . have precluded conclusions” about “[t]he relationship between genital talc use and ovarian cancer.”<sup>109</sup> Although the authors modeled certain hypothetical recall bias scenarios, they only did so using their imputed results, which, for reasons already discussed, are inflated and unreliable. Even in these models, certain recall bias scenarios did nullify the imputed association. Ultimately, the authors concluded that “there is still uncertainty as to how much recall bias and missing data could upwardly bias effect estimates.”<sup>110</sup> Accordingly, plaintiffs’ experts are drawing “conclusions that study authors were not willing to make.” *In re Acetaminophen I*, 2023 U.S. Dist. LEXIS 224899, at \*105; *see also In re Onglyza*, 93 F.4th at 346

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<sup>108</sup> (E.g., McTiernan 3d Am. Rep. at 53; Addendum to Rep. of Bernald L. Harlow (“Harlow Add. Rep.”), May 28, 2024 (Ex. 52 to Davidson Decl.); Cote Am. Rep. at 25.)

<sup>109</sup> O’Brien 2024 at 1.

<sup>110</sup> *Id.* at 14.

(excluding expert, who “drew ‘unauthorized . . . conclusions the authors of the study d[id] not make,’ betraying a ‘lack of scientific rigor’”) (citation omitted).

Plaintiffs’ experts also fail to meaningfully address whether the small association reported in case-control studies could be explained by confounding, which occurs when another causal factor confuses the relationship between the agent of interest and outcome of interest. *See RMSE* at 591. Drs. Clarke-Pearson and Harlow ignore this issue in their reports.<sup>111</sup> *See In re Acetaminophen I*, 2023 U.S. Dist. LEXIS 224899, at \*99 (excluding expert who “repeatedly ignores authors’ cautions that familial or genetic confounding may explain . . . the observed association”). To the extent that Drs. Singh, Smith, Smith-Bindman, Siemiatycki, Wolf, McTiernan and Cote address this concept, they downplay it as not a real problem because “the studies reviewed” “all adjusted for potential confounding factors.”<sup>112</sup> That is an oversimplification of the issue because “all of

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<sup>111</sup> (Clarke-Pearson 3d Am. Rep. (not discussing confounding); Harlow Rep. (not discussing confounding); Dep. of Bernard L. Harlow (“4/9/24 Harlow Dep.”) 114:19-24, Apr. 9, 2024 (Ex. 53 to Davidson Decl.) (“Q. Do you discuss anywhere in your report any of the potential confounders that are listed in the studies that you reviewed looking at talcum powder use and ovarian cancer? A. I don’t believe I discussed it in the report . . . .”).)

<sup>112</sup> (McTiernan 3d Am. Rep. at 16, 27; *see also, e.g.*, Singh Suppl. Rep. at 6 (“[S]tudies were conducted by various investigators in various settings during various time periods thus reducing the possibility of a confounding or bias as an explanation of an increased risk across all these studies.”); Siemiatycki 3d Am. Rep. at 67-68 (similar); Smith-Bindman 3d Am. Rep. at 9 (similar); Smith Rep. at 16 (only stating that “confounding bias in case-control studies appear to have

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the factors that might make someone susceptible to developing ovarian cancer are not currently known.”<sup>113</sup> *See In re Acetaminophen II*, 2024 U.S. Dist. LEXIS 121259, at \*56-57 (dismissing confounding as not “‘the most likely’ explanation for any apparent association . . . does not reflect the rigor required to render an admissible opinion on causation”). Even more importantly, it is just not true. Most of the studies do not adjust for all potential confounders, such as douching, which sometimes accompanies perineal talc use.<sup>114</sup>

The only expert who attempts to meaningfully discuss douching as a

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minimal impact”); Wolf 3d Am. Rep. at 11 (same); Cote Am. Rep. at 25 (“While there is always the potential that there are other, unknown factors that may confound the relationship between genital talc use and ovarian cancer, it is unlikely.”).)

<sup>113</sup> (See Dep. of Jack Siemiatycki (“1/31/19 Siemiatycki Dep.”) 173:6-9, Jan. 31, 2019 (Ex. 54 to Davidson Decl.); *see also* Dep. of Judith K. Wolf (“9/14/21 Wolf Dep.”) 534:5-9, Sept. 14, 2021 (Ex. 55 to Davidson Decl.) (acknowledging that for all cancers there is a “possibility of factors that are, as of now, unknown”); Dep. of Rebecca Smith-Bindman (“2/8/19 Smith-Bindman Dep.”) 306:17-20, Feb. 8, 2019 (Ex. 56 to Davidson Decl.) (admitting that it is “impossible to say that all known and unknown confounding factors have been controlled for in any given study”); Dep. of Sonal Singh (“1/16/19 Singh Dep.”) 237:24-238:12, Jan. 16, 2019 (Ex. 57 to Davidson Decl.) (“Residual confounding is possible because you can’t measure . . . every variable that you can think of.”).)

<sup>114</sup> *See* Gonzalez 2016 at 797 (“Douching was more common among talc users[.]”); *see also* Chang 2024 at 5 (noting “[f]or the hygiene mixture”—which includes, *inter alia*, shower gel, deodorant, genital talc use and douche—“a positive association with ovarian cancer incidence” was observed “with douche as the most important component”); Dep. of Daniel L. Clarke-Pearson (“3/8/24 Clarke-Pearson Dep.”) 383:3-9, Mar. 8, 2024 (Ex. 58 to Davidson Decl.) (“douching contributed significantly to the overall hazard ratio in” Chang 2024).

potential confounder is Dr. Moorman, who cites to Gabriel 2019—an article co-authored by multiple plaintiffs’ experts in talcum powder litigation—as evidence “against the notion that the association between talc use and ovarian cancer is due to uncontrolled confounding.”<sup>115</sup> But that article reported conflicting data, for example, a negative association for women who both ever used talc and homemade douches regularly (OR: 0.83; 95% CI: 0.52-1.33), and a small statistically significant increased risk for women who both ever used talc and homemade douches regularly (OR: 1.53; 95% CI: 1.11-2.10).<sup>116</sup> And although Dr. Moorman claims that the Gonzalez 2016 study “showed that adjusting for douching using statistical modelling had a negligible effect on the association between talc use and ovarian cancer,”<sup>117</sup> the authors of that study clearly reported that douching (unlike talc) was associated with increased cancer risk and stated that “[i]f douching is a risk factor for ovarian cancer, some of the earlier reports on talc could have been subject to confounding bias.”<sup>118</sup> Accordingly, Dr. Moorman’s conclusions about potential confounding by douching are “unauthorized” by the data she cites,

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<sup>115</sup> (Moorman Suppl. Rep. at 3-4.)

<sup>116</sup> Gabriel, *Douching, Talc Use, and Risk for Ovarian Cancer and Conditions Related to Genital Tract Inflammation*, 28(11) *Cancer Epidemiol. Biomarkers Prev.* 1835 (2019) (“Gabriel 2019”) (Ex. 59 to Davidson Decl.).

<sup>117</sup> (Moorman Rep. at 28.)

<sup>118</sup> Gonzalez 2016 at 800.

“betraying ‘a lack of scientific rigor.’” *In re Onglyza*, 93 F.4th at 346 (citation omitted).

For all of these reasons, plaintiffs’ experts’ opinions regarding “strength of association” defy the clear statements of their own cited studies and are unscientific. This alone requires exclusion of their Bradford Hill analyses.

## II. PLAINTIFFS’ EXPERTS USE UNRELIABLE METHODOLOGIES TO CONCLUDE THAT THE EPIDEMIOLOGY STUDIES ARE CONSISTENT.

“Next on my list of features to be specially considered I would place the consistency of the observed association. Has it been repeatedly observed by different persons, in different places, circumstances and times?”<sup>119</sup>

Consistency is important because “[d]ifferent studies that examine the same exposure-disease relationship generally should yield similar results.”<sup>120</sup> Here, studies have **not** consistently shown an association between perineal talc use and ovarian cancer, as the NCI, FDA and the studies themselves have recognized.<sup>121</sup>

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<sup>119</sup> Hill 1965 at 8.

<sup>120</sup> *RMSE* at 604.

<sup>121</sup> See NCI 2024 PDQ (“Results from case-control and cohort studies are **inconsistent** . . .”) (emphasis added); FDA Denial Letter at 4 (case-control studies “do not demonstrate a consistent positive association”); Lynch, *Systematic Review of the Association Between Talc and Female Reproductive Tract Cancers*, 5 *Frontiers in Toxicology* 1, 7 (2023) (“Lynch 2023”) (Ex. 60 to Davidson Decl.) (“None of the five prospective cohort studies reported any statistically significant associations between genital talcum powder use and risk of epithelial ovarian cancer, and relative risk estimates were close to unity.”) (citations omitted);

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Neither the cohort nor hospital-based case-control studies show a statistically significant association, leaving only population-based case-control studies.<sup>122</sup> And as Dr. Moorman acknowledged, even among that subset of studies, only approximately half reported a statistically significant increased risk of ovarian cancer.<sup>123</sup> These findings are the opposite of consistent data. Plaintiffs' experts admit this factor is important,<sup>124</sup> but attempt to brush aside the inconsistencies in the relevant epidemiology by: (1) ignoring, criticizing or selectively interpreting

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Goodman 2024 at 3 (“Cohort studies have consistently reported no overall association and no exposure-response relationship between perineal talc use and ovarian cancer risk overall.”); Micha 2022 at 932 (“Since clinical research has accorded inconsistent findings, . . . an unequivocal conclusion that the observed associations between talc powder and ovarian cancer are causal remains untenable”).

<sup>122</sup> See Lynch 2023 at 7. (*See also, e.g.,* McTiernan 3d Am. Rep. at 61 (“Results of the Nurses’ Health Study and Women’s Health Initiative cohort studies were overall attenuated compared with results of the case-control studies.”).)

<sup>123</sup> (2/13/24 Moorman Dep. 93:1-23.) *See also* Penninkilampi 2018 at 46 fig. 2.

<sup>124</sup> (*E.g.,* McTiernan 3d Am. Rep. at 97-98 (“high weight” on consistency); Clarke-Pearson 3d Am. Rep. at 13 (considers consistency to be “critically important”); Kane Rep. at 34 (considers consistency to be an “important factor”); Cote Am. Rep. at 6 (consistency “strongly weighted”); Siemiatycki 3d Am. Rep. at 70-73 (consistency “[h]ighly important”); Singh Suppl. Rep. at 2 (strength and consistency factors “carried the most weight”); Smith Rep. at 20 (“Strength and consistency are very important to a physician involved in patient care.”); Wolf 3d Am. Rep. at 19 (“deem[s] the consistency and replication of the studies to be important in . . . causation analysis”).)

the cohort study data; and (2) dismissing statistical significance as irrelevant. This further highlights the unreliability of their opinions.

**A. Plaintiffs’ Experts Attack The Cohort Studies In An Attempt To Find Consistency.**

Plaintiffs’ experts’ proffered bases for discounting the overwhelming majority of studies reporting no statistically significant association between cosmetic talc and ovarian cancer repeat the same results-oriented approach that led to Drs. McTiernan and Moorman being excluded by the *Zantac* court. *See In re Zantac*, 644 F. Supp. 3d at 1201 (rejecting Drs. McTiernan and Moorman’s “critique [of more pertinent studies, which] amounts to speculation, and it runs counter to every published study to have considered the subject”).

*First*, plaintiffs’ experts theorize that the cohort studies did not show a statistically significant association because they did not have a large enough sample size—i.e., they lacked sufficient statistical power.<sup>125</sup> Even assuming this claim had any scientific basis during the original Rule 702 proceeding (which it did not),<sup>126</sup> it is now foreclosed by the more recent results of O’Brien 2020, which

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<sup>125</sup> (E.g., McTiernan 3d Am. Rep. at 61-62; Smith Rep. at 20; Dep. of Arch Carson (“1/19/19 Carson Dep.”) 251:17-253:3, Jan. 19, 2019 (Ex. 61 to Davidson Decl.); Moorman Rep. at 24-25; Siemiatycki 3d Am. Rep. at 16-17; Singh Rep. at 16; Wolf 3d Am. Rep. at 6; 3/21/24 Cote Dep. 264:20-265:18.)

<sup>126</sup> A 2018 meta-analysis specifically considered whether low statistical power could explain why the relevant cohort studies do not show an association between perineal talc use and ovarian cancer and rejected that theory. Berge 2018 at 253

(cont’d)

pooled four high-quality, long-term cohort studies that collectively followed **250,000** women who reported using talc in the genital area (more than would be required to detect even a small increased risk) and found that there was no statistically significant association between perineal talc use and the development of ovarian cancer. As noted above, the estimated HR for long-term use vs never use was 1.01 (95% CI, 0.82-1.25), with a non-statistically significant estimated HR of 1.09 (95% CI, 0.97-1.23) for frequent vs never users.<sup>127</sup> The fact that the largest epidemiological study to ever assess the proposed relationship found no statistically significant association puts the lie to plaintiffs' experts' claim that the cohort studies lack sufficient power.

Several expert witnesses cite a calculation set forth in a commentary by Narod 2016,<sup>128</sup> which stated that the studies would need to examine at least 200,000 total participants for 10 years to detect a statistically significant relative

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("[T]he statistical power of the meta-analysis of these cohort studies to detect a RR of 1.25, similar to the result of the meta-analysis of case-control studies, was 0.99. Thus, low power of cohort studies cannot be invoked as [an] explanation of the heterogeneity of results.").

<sup>127</sup> O'Brien 2020 at 49, 57 ("In this analysis of pooled data from women in 4 US cohorts, there was not a statistically significant association between use of powder in the genital area and incident ovarian cancer."); *see also* Gossett 2020 at 29-30 (The O'Brien study "represents the largest cohort to date to examine whether an association exists between powder use in the genital area and ovarian cancer risk.").

<sup>128</sup> (See Moorman Rep. at 25; Smith Rep. at 20; Wolf 3d Am. Rep. at 6.)

risk of 1.2.<sup>129</sup> Dr. McTiernan conducted her own calculation and similarly concluded that the cohort studies would need to have more than 140,000 cohort participants to detect a statistically significant relative risk of 1.24.<sup>130</sup> But O'Brien 2020 pooled cohort studies that collectively followed 250,000 women who reported using talc in the genital area for an average of more than 11 years, easily surpassing these supposed thresholds.<sup>131</sup>

While plaintiffs' experts nonetheless point to a statement from the O'Brien authors cautioning that the results might lack sufficient power to identify a slight increase in risk,<sup>132</sup> the study addressed hundreds of thousands of women, making it the "largest study of this topic to date."<sup>133</sup> Indeed, the sheer size and robustness of the study specifically led the editorial accompanying the O'Brien article to label the results "overall reassuring."<sup>134</sup> Notably, although there are mathematical

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<sup>129</sup> Narod, *Talc and Ovarian Cancer*, 141(3) Gynecol. Oncol. 410, 411 (2016) ("Narod 2016") (Ex. 62 to Davidson Decl.); *see also* 9/13/21 Wolf Dep. 174:2-18 ("[Q.] The pooled study includes 252,745 women, correct? A. Yes. Q. That is more women than you believe need to be studied to accurately predict the risk associated with talc use and ovarian cancer, correct? A. Yes. . . . Dr. Narod, who I know I quoted in my report, estimated that it would take 200,000 women, and this one has more than that.") (objection omitted).

<sup>130</sup> (McTiernan 3d Am. Rep. at 61.)

<sup>131</sup> *See* O'Brien 2020.

<sup>132</sup> (E.g., McTiernan 3d Am. Rep. at 75; Cote Am. Rep. at 18; Singh Supp. Rep. at 17.)

<sup>133</sup> O'Brien 2020 at 56.

<sup>134</sup> Gossett 2020 at 30.

techniques for calculating statistical power (i.e., the ability of a survey to discover a real association) none of plaintiffs' experts undertook any power assessment of O'Brien. That is presumably because its robust analysis satisfies the threshold number of participants proposed by both the Narod commentary and Dr. McTiernan. In short, the cohort studies had the power to detect a statistically significant risk if it existed—and their failure to do so means that Dr. McTiernan's and the other experts' power-based criticisms are not grounded in reliable science.

Plaintiffs' experts also attempt to show consistency by suggesting that subgroup analyses within the cohort studies are consistent with the case-control studies. For example, although O'Brien 2020 found that there was no statistically significant association between perineal talc use and the development of ovarian cancer,<sup>135</sup> plaintiffs' experts purport to rely on a "subgroup analysis" in O'Brien 2020 that found a very small, but statistically significant, association for women with a patent reproductive tract (i.e., women with an intact uterus who had not undergone tubal ligation) (HR: 1.13; 95% CI: 1.01-1.26).<sup>136</sup> As the O'Brien 2020 authors explained, however, the reported weak "association [with patent

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<sup>135</sup> O'Brien 2020 at 49, 57 ("In this analysis of pooled data from women in 4 US cohorts, there was not a statistically significant association between use of powder in the genital area and incident ovarian cancer.").

<sup>136</sup> (E.g., Clarke-Pearson 3d Am. Rep. at 9; Wolf 3d Am. Rep. at 11; Smith-Bindman 3d Am. Rep. at 30-31; Singh Suppl. Rep. at 2; Moorman Suppl. Rep. at 15; McTiernan 3d Am. Rep. at 9.)

reproductive tracts] was not significantly different from that observed in women with nonpatent reproductive tracts” (i.e., the confidence intervals for the two associations overlapped).<sup>137</sup> An accompanying editorial confirmed that “there are no significant differences in the HRs in the patent . . . and nonpatent subgroups,” which “confirms the overall conclusion that there is no demonstrable statistically significant association between use of powder in the genital area and ovarian cancer risk.”<sup>138</sup> The editorial further warned that “statistically unsophisticated reader[s]” “should not . . . selectively highlight[]” the results for patent women;<sup>139</sup> yet, that is exactly what plaintiffs’ experts do.

Plaintiffs’ experts also contend that O’Brien 2024’s re-analysis of the results from the Sister Study demonstrates “high consistency with results from case-control, pooled analyses, and meta-analyses.”<sup>140</sup> Essentially, plaintiffs’ experts reason that the original Sister Study should be ignored because after the O’Brien 2024 authors imputed a number of “corrections” and assumptions into the Sister Study cohort data, they reported “evidence supporting a positive association

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<sup>137</sup> O’Brien 2020 at 56.

<sup>138</sup> Gossett 2020 at 30 (emphasis added).

<sup>139</sup> *Id.*

<sup>140</sup> (E.g., McTiernan 3d Am. Rep. at 54; *see also id.* 47-55, 62; Cote Am. Rep. at 27-28; Harlow Add. Rep.; Siemiatycki 3d Am. Rep. at 53-55.)

between ever genital talc use and incident ovarian cancer.”<sup>141</sup> Needless to say, consistency cannot be achieved by replacing actual data with imputations (i.e., guesses). The *actual* data generated by the Sister Study cohort show an “inverse or weakly positive associations between [talc] and all cancers of interest.”<sup>142</sup> And as discussed above, the only non-imputed prospective data in the study reported no association. Thus, at most, O’Brien 2024 highlights inconsistencies in the body of literature, and plaintiffs’ experts’ willingness to reach conclusions that the O’Brien authors “d[id] not make” “betray[s] a ‘lack of scientific rigor.’” *In re Onglyza*, 93 F.4th at 346 (citation omitted).

Plaintiffs’ experts also criticize the cohort studies for having supposedly insufficient follow-up periods given the putative latency period of ovarian cancer.<sup>143</sup> But this argument is speculative for several reasons. First, women did not begin using talc when they enrolled in cohort studies, and plaintiffs’ own experts have recognized that women typically begin using talc perineally at a

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<sup>141</sup> O’Brien 2024 at 13.

<sup>142</sup> *Id.* at 12; *see also* Gonzalez 2016 at 800-02 (HR 0.73 (95% CI: 0.44-1.2)).

<sup>143</sup> (*E.g.*, Dep. of Anne McTiernan (“1/28/19 McTiernan Dep.”) 226:20-227:17, Jan. 28, 2019 (Ex. 63 to Davidson Decl.) (criticizing cohort studies for “not follow[ing] the women for very long”); 1/31/19 Siemiatycki Dep. 169:19-172:6 (testifying that, among other biases, “short follow-up periods . . . would be a source of bias in cohort studies”); Wolf 3d Am. Rep. at 8 (similar).)

young age.<sup>144</sup> Second, nobody (including plaintiffs’ experts) knows what the latency period is for ovarian cancer,<sup>145</sup> and “nothing in either *Daubert* or the Federal Rules of Evidence requires a district court to admit opinion evidence that is connected to existing data only by the *ipse dixit* of the expert.” *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997). And third, the notion that the cohort studies reflect only limited spans of talc use is false. O’Brien 2020—the largest and most recent pooled analysis of cohort studies—included several additional years of follow-up for each of the studies criticized by plaintiffs’ experts, resulting in average follow-up times of 33.2 years for NHS; 9.6 years for Sister Study; and 17.4 years for WHI. Overall, the mean follow-up time for the more than 250,000

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<sup>144</sup> Cramer, *The Association Between Talc Use and Ovarian Cancer: A Retrospective Case-Control Study in Two US States*, 27(3) *Epidemiology* 334, 335 (2016) (“Cramer 2016”) (Ex. 64 to Davidson Decl.) (reporting that the “average age women began using talc was 20.0 for cases and 19.8 for controls”). The age at enrollment for the cohort studies is much older. See O’Brien 2020 at tbl. 1 (mean age and age range “at assessment for use of powder”).

<sup>145</sup> See Hanchette, *Ovarian Cancer Incidence in the U.S. and Toxic Emissions from Pulp and Paper Plants: A Geospatial Analysis*, 15(8) *Int’l J. Environ. Res. Public Health* 1619, 1619 (2018) (“Hanchette 2018”) (Ex. 65 to Davidson Decl.) (noting that latency period for ovarian cancer is unknown). (See also, e.g., 3/8/24 Clarke-Pearson Dep. 341:13-20 (opining latency can be longer or shorter than 30 years); 1/16/19 Singh Dep. 171:3-6 (“I don’t know a specific number. It’s, you know, several years”); 1/19/19 Carson Dep. 168:7-9 (testifying that the latency period for ovarian cancer is 20-40 years); Dep. of Judith K. Wolf (“1/7/19 Wolf Dep.”) 325:23-327:4, Jan. 7, 2019 (Ex. 66 to Davidson Decl.) (testifying that the latency period could be 15 to 20 years, but she “d[idn’t] know the latency period for sure”).)

women included in O'Brien 2020 was 11.2 years (longer than Narod felt would be necessary).<sup>146</sup> Even with these extended follow-up times, O'Brien 2020 still did not find a statistically significant association between perineal talc use and the development of ovarian cancer.<sup>147</sup> Accordingly, O'Brien 2020 puts to rest any concerns about latency.

Plaintiffs' experts additionally criticize the cohort studies for supposedly failing to accurately ascertain enrollees' talc use for various reasons, principally arguing that they did not ask sufficiently specific questions about talc use to gather meaningful exposure data<sup>148</sup> and potentially misclassified participants as talc users or non-talc users because they did not repeatedly update survey data on talc use.<sup>149</sup> But any concerns about imprecise exposure data would apply to case-control studies as well, reinforcing plaintiffs' experts' "propensity to cherry-pick" the studies that support their conclusions. *Daniels-Feasel v. Forest Pharms., Inc.*, No. 17-4188, 2021 WL 4037820, at \*9 (S.D.N.Y. Sept. 3, 2021) (excluding expert

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<sup>146</sup> O'Brien 2020 at 49. (See also 9/21/21 Siemiatycki Dep. 123:16-22 (agreeing that O'Brien 2020 included "[l]onger follow-up than the previously published individual [cohort] studies").)

<sup>147</sup> See O'Brien 2020 at 57 (highlighting "long follow-up time," which included "2168 ovarian cancer cases that developed over 3.8 million person-years," "far exceed[ing] a previous meta-analysis of the published" individual studies).

<sup>148</sup> (E.g., McTiernan 3d Am. Rep. at 60-61; Smith Rep. at 16.)

<sup>149</sup> (E.g., Smith-Bindman 3d Am. Rep. at 18-19; Singh Rep. at 11-12.)

who “disregard[ed] . . . studies that do not support his conclusions because they suffer from the same limitations” that apply to his touted studies), *aff’d*, No. 22-146, 2023 WL 4837521 (2d Cir. July 28, 2023).<sup>150</sup>

While the Court previously dismissed defendants’ challenges as “disput[ing] the experts’ conclusions and interpretations of the different studies, not the experts’ methodologies,” *In re Johnson & Johnson*, 509 F. Supp. 3d at 171-72, “conclusions and methodology are not entirely distinct from one another,” *In re Paraquat*, 2024 WL 1659687, at \*40 (quoting *Joiner*, 522 U.S. at 146); *see also In re Acetaminophen II*, 2024 U.S. Dist. LEXIS 121259, at \*44 (same). In any event, as illustrated above, defendants are challenging plaintiffs’ experts’ disregard of divergent data across both similarly and differently designed studies, including more recent studies that were not addressed in the prior ruling—e.g., O’Brien 2020. Third Circuit caselaw has long recognized that such an approach to consistency “undermines reliability” (i.e., is a matter of admissibility rather than

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<sup>150</sup> Any concern that alleged misclassification artificially reduces relative risks is likewise speculative. This argument requires an assumption that participants in cohort studies initially reported that they did not use talc, but later became talc users (in sufficient quantity to cause cancer). Such usage patterns are highly improbable because, as noted above, most talc users begin using talc by their mid-20s and that the mean duration of talc use is greater than 20 years. *See, e.g., Wu, African Americans and Hispanics Remain at Lower Risk of Ovarian Cancer Than Non-Hispanic Whites after Considering Nongenetic Risk Factors and Oophorectomy Rates*, 24(7) Cancer Epidemiol. Biomarkers Prev. 1094, 1097 tbl. 2 (2015) (“Wu 2015”) (Ex. 67 to Davidson Decl.) (showing mean talc use of more than 20 years across all groups); *see also* Cramer 2016.

weight), *see In re Zolofit*, 858 F.3d at 800, and that precept has only been cemented by the recent amendments to Rule 702, *see In re Acetaminophen I*, 2023 U.S. Dist. LEXIS 224899, at \*80 (excluding expert for “wholesale failure to address the highly heterogenous nature of the studies or the inconsistencies between results that do address the same outcomes”).

In short, plaintiffs’ criticisms of the cohort study data—and subsequent disregard for only the cohort data that does not support their causation opinions—are unreliable.

**B. Plaintiffs’ Experts Improperly Disregard Statistical Significance In Reaching Their Conclusions On Consistency.**

In an effort to bolster their claims that the epidemiological data are consistent, plaintiffs’ experts also attack statistical significance as “outdated,” “irrelevant” and “moot.”<sup>151</sup> This position further highlights the unreliable nature of their analyses. For starters, it is not only statistical significance that renders the results inconsistent, because *point estimates* (which have nothing to do with

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<sup>151</sup> (Dep. of Rebecca Smith-Bindman (“3/20/24 Smith-Bindman Dep.”) 27:21-28:8, Mar. 20, 2024 (Ex. 68 to Davidson Decl.) (claiming statistical significance is “outdated”); Siemiatycki 3d Am. Rep. at 72-73 (stating that he is “impressed by the consistently elevated risk across studies” because “[a]lmost all of the 30 or so studies have produced an RR greater than the null [neutral] value of 1.0”; it is “irrelevant” that “individual study RRs are not all necessarily statistically significant”); 3/27/24 Siemiatycki Dep. 226:18-20 (“Whether the individual studies are statistically significant at point .05 level or not is moot. It’s not the important thing.”).)

significance) are consistently lower in cohort studies than case-control studies. Just as importantly, however, courts have time and again rejected arguments by plaintiffs' experts that statistical significance should be thrown out the window. *See, e.g., In re Paraquat*, 2024 WL 1659687, at \*38 (excluding an expert who "fail[ed] to engage" with the "lack of statistical significance . . . throughout the epidemiological literature") (citing *In re Acetaminophen I*); *In re Acetaminophen II*, 2024 U.S. Dist. LEXIS 121259, at \*68 ("[I]gnor[ing] statistical significance . . . is not a reliable application of scientific methodology."); *In re Zolof*, 858 F.3d at 793, 799 (affirming exclusion of expert who "classified insignificant odds ratios above one as supporting a 'consistent' causality result, downplaying the possibility that they support *no* association"). As one court recently explained, "it is not for the courts to be the pioneers, forging new trails in scientific thinking, especially when that means departing from well-established research principles, such as the principle of statistical significance." *In re Acetaminophen I*, 2023 U.S. Dist. LEXIS 224899, at \*122 (citation omitted).

Notably, just months before the recent amendments took effect, the *Zantac* court excluded Drs. McTiernan and Moorman for "routinely . . . disregard[ing] the concept of statistical significance." *In re Zantac*, 644 F. Supp. 3d at 1222; *id.* at 1237-38 ("[The expert]'s reliance on statistically insignificant results is routine.") (footnote omitted). Similarly, the Fourth Circuit affirmed the exclusion of Dr.

Singh’s general causation opinion regarding the drug Lipitor because the plaintiffs “failed to demonstrate that Dr. Singh’s reliance on non-statistically significant ‘trends’ is accepted in [the] field” or has “served as the basis for any epidemiologist’s causation opinion in peer-reviewed literature.” *In re Lipitor*, 892 F.3d at 641-42 (citation omitted).

Plaintiffs’ experts have taken the same methodologically unsound approach here. They attest that the consistency consideration is satisfied because “nearly all point estimates show[] a direction of increased risk of ovarian cancer.”<sup>152</sup> But that conclusion effectively ignores statistical significance because many of the studies that reported a so-called “positive” association over 1 ***are not statistically significant***.<sup>153</sup> This is particularly problematic because, as explained above, the reported weak association in select population-based case-control studies can be

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<sup>152</sup> (Singh Rep. at 63; *see also, e.g.*, Siemiatycki 3d Am. Rep. at 72 (“Almost all of the 30 or so studies considered have produced an RR greater than the null value of 1.0.”); Cote Am. Rep. at 5 (opining the cohort studies and 19 “of the 23 case-control studies” reported “positive association[s]”); Harlow Rep. at 20 (“[N]one of the non-causal explanations can account adequately for the consistent positive association across so many studies.”); Kane Rep. at 11 (“vast majority” of studies “find an association”); McTiernan 3d Am. Rep. at 46, 97 (“[o]f the 28 [case-control] studies, 24 found odds ratios greater than 1.1” and opining that “8 studies did not have statistically significant results, [but] provide relevant data because their relative risk estimates were consistent with the 16 studies that showed statistically significant results”).)

<sup>153</sup> *See* Penninkilampi 2018 at 46 fig. 2. (*See also* 2/13/24 Moorman Dep. 93:1-5 (“Q. So that means 11 out of 24 case-control studies did not show a significant association, right? A. Not a statistically significant increased risk, yes.”).)

attributed to recall bias and/or confounding, meaning that any such association is already inflated. Indeed, as Dr. Harlow admitted, “when the odds ratio or relative risk does not include 1, then there is . . . much more certainty that the true association is greater than 1.”<sup>154</sup>

In its prior ruling, the Court reasoned that Drs. McTiernan, Carson and Clarke-Pearson could “g[i]ve weight to positive, non-significant results” because Dr. Kenneth Rothman (a frequent consultant for plaintiffs in tort litigation and co-author of Dr. Harlow’s report) “opined . . . [that] inconsistent statistical significance from one study to the next does not, in [and] of itself, show inconsistency under Bradford Hill.” *In re Johnson & Johnson*, 509 F. Supp. 3d at 170-71.<sup>155</sup> However, the district court in *Zolof* specifically rejected “Rothman’s approach” as “[s]ailing against prevailing scientific breeze.” *In re Zolof*

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<sup>154</sup> (4/9/24 Harlow Dep. 187:21-24; *see also id.* 303:15-20 (“Q. But a confidence interval that includes 1 means that the real point estimate could be 1.0? A. It could be 1.0 . . . .”).) Dr. Wolf similarly agreed that “[n]ot finding statistical significance means that the authors could not reject the null hypothesis of no interaction.” (Dep. of Judith K. Wolf (“1/10/24 Wolf Dep.”) 155:15-23, Jan. 10, 2024 (Ex. 69 to Davidson Decl.); *id.* 171:24-172:13 (“Q. When a study cannot reject the null hypothesis because the confidence interval crosses 1, that means the finding could be due to chance; correct? . . . [A.] So . . . that could happen . . . .”) (objection omitted).)

<sup>155</sup> Plaintiffs’ experts similarly rely on Dr. Rothman’s statements to support their disregard for statistical significance. (*E.g.*, McTiernan 3d Am. Rep. at 129; Moorman Rep. at 38; 3d Am. Rep. of Laura M. Plunkett (“Plunkett 3d Am. Rep.”) at 108, May 28, 2024 (Ex. 70 to Davidson Decl.); Siemiatycki 3d Am. Rep. at 129; Singh Rep. at 85.)

(*Sertraline Hydrochloride*) Prods. Liab. Litig., MDL No. 2342, 2015 U.S. Dist. LEXIS 7664, at \*9 (E.D. Pa. Jan. 23, 2015) (quoting *DeLuca v. Merrell Dow Pharms., Inc.*, 911 F.2d 941, 946 (3d Cir. 1990), *abrogated on other grounds*, *In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717 (3d Cir. 1994)). In any event, defendants have never argued that statistical significance is a litmus test for consistency; rather, their point is that in undertaking the consistency analysis, an expert cannot simply ignore the statistically insignificant nature of purportedly positive results as plaintiffs' experts do here—i.e., “abandon the concept of statistical significance completely.” *In re Zantac*, 644 F. Supp. 3d at 1233; *see also In re Acetaminophen II*, 2024 U.S. Dist. LEXIS 121259, at \*69-70 (expert's consistency opinion “does not pass muster under Rule 702” where she “ignores the importance of statistical significance even in studies with large sample sizes”).

Moreover, plaintiffs' experts' treatment of statistical significance in their consistency analysis is at odds with their own approach elsewhere. For example, although Dr. Harlow agreed that “significance tests . . . increase the rigor of the conclusions drawn from data” and are “essential for interpreting the results of data analyses and enhancing the replicability of scientific results,” he nonetheless stated that these principles do not apply to “the use of statistical significance for making inferences about causation.”<sup>156</sup> In other words, Dr. Harlow's approach to statistical

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<sup>156</sup> (4/9/24 Harlow Dep. 366:7-24.)

significance “in the courtroom” does not reflect the “same level of intellectual rigor that” he uses in the “relevant field”—i.e., epidemiology. *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 152 (1999). And other experts selectively rely on statistical significance when it supports their opinions, such as Dr. Moorman, who opines that O’Brien 2020—which overall found no statistically significant association between perineal talc use and the development of ovarian cancer<sup>157</sup>—nonetheless supports her causation opinion because “there was a **statistically significant** increased risk of ovarian cancer among talc users in women with patent reproductive tracts.”<sup>158</sup> This is the quintessence of a “results-driven analysis.” *In re Acetaminophen I*, 2023 U.S. Dist. LEXIS 224899, at \*128-29 (“unstructured approach adopted by the plaintiffs’ experts permitted cherry-picking, allowed a results-driven analysis, and obscured the complexities, inconsistencies, and weaknesses in the underlying data”).<sup>159</sup>

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<sup>157</sup> O’Brien 2020 at 49, 57 (“In this analysis of pooled data from women in 4 US cohorts, there was not a statistically significant association between use of powder in the genital area and incident ovarian cancer.”).

<sup>158</sup> (Moorman Suppl. Rep. at 14 (emphasis added); *see also* 2/13/24 Moorman Dep. 86:1-13 (“[T]here is a statistical[ly] significant association with that one subgroup of women.”).)

<sup>159</sup> Several of plaintiffs’ experts also opine that consistency is satisfied because the talc meta-analyses have consistently reported an aggregate relative risk of roughly 1.2-1.3 (e.g., Clarke-Pearson 3d Am. Rep. at 13; Smith Rep. at 20; Cote Am. Rep. at 5; McTiernan 3d Am. Rep. at 8; Wolf 3d Am. Rep. at 11-12), but consistency among meta-analyses is not remarkable or meaningful. As Dr. Cote

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In sum, plaintiffs' experts seek to manufacture consistency by disregarding the bulk of the epidemiologic literature on grounds that O'Brien 2020 and other recent studies have rejected and by retiring the longstanding concept of statistical significance. These are the hallmarks of an unreliable approach to consistency.

**III. PLAINTIFFS' EXPERTS' OPINIONS THAT EPIDEMIOLOGICAL STUDIES SHOW A DOSE-RESPONSE CONTRADICT THE STUDY DATA AND SCIENTIFIC CONSENSUS.**

The dose-response factor assesses whether “a change in amount, intensity, or duration of exposure to an agent is associated with a change—either an increase or decrease—in risk of disease.” *McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1241-42 (11th Cir. 2005) (citation omitted). Dose-response is sorely lacking in the relevant literature, as recognized both by the NCI and FDA.<sup>160</sup>

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explains, because “data from these earlier [meta-analyses] are being reused” in later meta-analyses, any consistency is driven by the fact that they are all using the same data. (3/21/24 Cote Dep. 287:11-288:21.)

<sup>160</sup> NCI 2024 PDQ; FDA Denial Letter at 4. Even the Health Canada Assessment that has been touted (and potentially influenced) by plaintiffs and their experts reported that among “studies that provided some evidence of increased risk of ovarian cancer with increasing perineal applications of talc,” “none demonstrated both a clear dose-response trend and statistical significance.” Health Canada, *Final Screening Assessment: Talc (Mg<sub>3</sub>H<sub>2</sub>(SiO<sub>3</sub>)<sub>4</sub>)* (Chem. Abstracts Serv. Registry No. 14807-96-6) (Apr. 2021), at 33, <https://www.canada.ca/en/environment-climate-change/services/evaluating-existing-substances/screening-assessment-talc.html> (“Health Canada Screening Assessment”).

Plaintiffs' experts essentially concede that the dose-response factor is not satisfied but downplay its importance or distort the data as supporting a dose-response relationship. Neither approach is reliable.

**First**, a number of plaintiffs' experts have conceded that the relevant dose-response evidence is "equivocal" and "less compelling," and assert that it should therefore be given "lesser weight" in the causation analysis.<sup>161</sup> This approach is unscientific because dose-response is the "single most important factor to consider in evaluating whether an alleged exposure caused a specific adverse effect."

*McClain*, 401 F.3d at 1242 (citation omitted); *see In re Viagra*, 424 F. Supp. 3d at 796 ("Dr. Ahmed's dismissal of the importance of dose response evidence calls into further question the reliability of her Bradford Hill analysis."); *see also Chapman v. Procter & Gamble Distrib., LLC*, 766 F.3d 1296, 1308 (11th Cir. 2014) (describing dose-response as "indispensable" to establishing general causation). While the first *Daubert* ruling reasoned that "a strong dose-response is

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<sup>161</sup> (See, e.g., Kane Rep. at 35 ("equivocal"); Cote Am. Rep. at 37 ("moderate weight"); Singh Rep. at 65 ("less compelling"); Wolf 3d Am. Rep. at 19 ("less important factor"); Cote Am. Rep. 6 ("moderately weighted factor[]"); Smith-Bindman 3d Am. Rep. at 37 (noting that "this factor does not weigh[] heavily in [her] consideration"); Smith Rep. at 20 ("dose response can be helpful when determining causality, but not essential"); 2/13/24 Moorman Dep. 195:8-17 (admitting that dose response is "recognized as an area where more complete data would be desirable"); Dep. of Sonal Singh ("4/4/24 Singh Dep.") 67:3-25, Apr. 4, 2024 (Ex. 71 to Davidson Decl.) (explaining dose-response was evaluated to a "lesser" degree).)

not necessarily required for an expert to find a causal nexus,” *In re Johnson & Johnson*, 509 F. Supp. 3d at 179, it misread *Ferguson v. Riverside School District No. 416*, No. 00-0097, 2002 U.S. Dist. LEXIS 28851, at \*26 (E.D. Wash. Feb. 5, 2002). In *Ferguson*, “general causation [wa]s **not** at issue, and therefore . . . epidemiological studies [we]re not required” on the dose-response or other any other Hill criteria. *Ferguson*, 2002 U.S. Dist. LEXIS 28851, at \*26 (emphasis added). And to the extent the court addressed dose-response as part of specific causation, there was no “dispute that there is a general dose-response relationship for molds in that the stronger the dose the more likely any individual is to have an injury.” *Id.* at \*20.

Some plaintiffs’ experts also attempt to downplay the importance of dose-response by suggesting that the lack of precise data regarding the quantity of talcum powder used by study participants somehow obviates the need to establish a dose-response.<sup>162</sup> However, imprecision in the exposure data is a fundamental weakness of the literature that weigh **against** an epidemiologist inferring causation. *See In re Acetaminophen I*, 2023 U.S. Dist. LEXIS 224899, at \*89 (excluding epidemiologist’s opinion on dose-response when the witness “does not grapple

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<sup>162</sup> (See, e.g., Singh Rep. at 55 (“Ascertaining *dose response* relationship with talc and ovarian cancer is difficult because of the challenges in quantifying talcum powder use usually collected by self-reported data . . . .”); Clarke-Pearson 3d Am. Rep. at 13 (similar); Kane Rep. at 34-35 (similar); Moorman Rep. at 31 (similar); 1/28/19 McTiernan Dep. 53:18-22 (similar).)

with a key issue in the underlying studies: none were able to record the actual dosages taken by pregnant women”). Any suggestion otherwise would effectively “reverse[] the burden of proof” by requiring defendants to disprove the existence of a dose-response relationship, which is not the law. *See In re Onglyza*, 93 F.4th at 345 (excluding opinion that the literature “should be interpreted as cause-and-effect unless there is compelling evidence to prove otherwise”) (citation omitted).

**Second**, some of plaintiffs’ experts half-heartedly attempt to manufacture a dose-response relationship by twisting the epidemiologic data. For example, several experts contend that the Terry 2013 pooled analysis shows a dose-response,<sup>163</sup> even though the authors of that study disclaimed having found a dose-response, stating that they “observed no significant trend . . . in risk with increasing number of lifetime applications.”<sup>164</sup> The Court previously reasoned that because Terry “did not wholly rule out a dose-response relationship,” the evidence on this Hill factor was “inconclusive” such that Drs. McTiernan, Clarke-Pearson and Carson could opine on general causation. *In re Johnson & Johnson*, 509 F. Supp. 3d at 180. However, that once again confuses the relevant burden, *see* Fed. R. Evid. 702; *see also In re Onglyza*, 93 F.4th at 345 (excluding opinion that the

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<sup>163</sup> (E.g., McTiernan 3d Am. Rep. at 9, 71; Siemiatycki 3d Am. Rep. at 46; Smith-Bindman 3d Am. Rep. at 29; Smith Rep. at 20; Wolf 3d Am. Rep. at 19; Plunkett 3d Am. Rep. at 52; Clark-Pearson 3d Am. Rep. at 13.)

<sup>164</sup> Terry 2013 at 811.

literature “should be interpreted as cause-and-effect unless there is compelling evidence to prove otherwise”) (citation omitted). And even more importantly, it elides the critical methodological problem of plaintiffs’ experts not just exceeding the limits of their cited data but also “misrepresent[ing]” them. *See In re Acetaminophen II*, 2024 U.S. Dist. LEXIS 121259, at \*68 (excluding expert who “misrepresents statements by the authors of the studies upon which she relies.”).

Dr. McTiernan asserts that Mills 2004 demonstrated “a statistically significant trend . . . in the dose-response analysis,”<sup>165</sup> even though the study’s own *abstract* says the opposite, flatly stating “no dose response was found.” And although Dr. McTiernan also claims that Taher 2019 provides data that is “indicative of dose-response,”<sup>166</sup> that study found that women who used talc for 20-plus years did not have a statistically significant association, whereas women who used talc less than 20 years had a both a higher point estimate and statistically significant risk ratio.<sup>167</sup>

Plaintiffs’ experts also cite several meta-analyses (including Penninkilampi 2018 and Berge 2018) and the Schildkraut 2016 study as supposedly showing

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<sup>165</sup> (McTiernan 3d Am. Rep. at 39.)

<sup>166</sup> (McTiernan 3d Am. Rep. at 100.)

<sup>167</sup> Taher 2019 at 93 tbl. 2. (*See also* 2/13/24 Moorman Dep. 94:24-95:10 (admitting there was “a high degree of uncertainty” in Taher 2019’s dose-response findings).)

evidence of a dose-response.<sup>168</sup> But the Penninkilampi 2018 meta-analysis and Schildkraut 2016 study arbitrarily grouped users into only two categories and then found statistically significant associations for the higher use category. That is not meaningful evidence of dose-response. And although Berge 2018 reported a “weak” dose-response trend, the authors cautioned that these data came from a small number of case-control studies, not the full panoply of relevant evidence.<sup>169</sup>

In short, plaintiffs’ experts are claiming that a dose-response existed even though “no study [has] concluded such a relationship existed, with some even observing the inverse of a dose-response relationship.” *In re Zantac*, 644 F. Supp. 3d 1239-40 (excluding Dr. McTiernan for taking a similar approach to dose-response).

**Finally**, several of plaintiffs’ experts hypothesize that the dose-response for talc and ovarian cancer may not be “monotonic” or “linear,” but rather may be a “threshold” response—i.e., a risk that uniformly increases after a certain minimal level of exposure.<sup>170</sup> But this is pure speculation because none of plaintiffs’

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<sup>168</sup> (E.g., McTiernan 3d Am. Rep. at 35, 46; Siemiatycki 3d Am. Rep. at 19; Clark-Pearson 3d Am. Rep. at 13; Smith-Bindman 3d Am. Rep. at 37.)

<sup>169</sup> See Berge 2018 at 253.

<sup>170</sup> (See, e.g., Moorman Rep. at 31 (one “possible reason[] why not all studies observed dose-response relationships” is because “the dose-response relationship may not be a simple linear trend”); Wolf 3d Am. Rep. at 18 (similar); Clarke-Pearson 3d Am. Rep. at 13 (“asbestos exposure and mesothelioma is generally

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experts is able to estimate what the putative threshold is, much less opine on what level or amount of exposure over time is enough to cause cancer.<sup>171</sup> In any event, if there really were a threshold effect, studies would reflect a consistently increased risk over a certain threshold; yet, the studies report highly inconsistent (and even decreasing) risks.<sup>172</sup>

In short, the evidence on dose-response is not just “equivocal”; it forecloses the existence of such a relationship, which is why plaintiffs’ experts try to

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thought to have a ‘threshold response’”); *see also* Siemiatycki 3d Am. Rep. at 54 (“[E]xposure to talc powder in the 20s and 30s may be a critical or particularly vulnerable period in a woman’s life for risk from talc exposure.”).)

<sup>171</sup> (E.g., Dep. of Judith K. Wolf (“4/25/24 Wolf Dep.”) 63:10-16, Apr. 25, 2024 (Ex. 72 to Davidson Decl.) (“I’m not aware of any study that’s reported on any particular threshold for any type.”); 4/9/24 Harlow Dep. 150:9-22 (“I don’t believe there is a known dose that needs to be present for there to be a risk . . . .”); 4/9/24 Harlow Dep. 152:2-7 (“I do not have an opinion that there is a particular amount of exposure that is necessary to put a woman at greater risk of ovarian cancer, but that the risk increases with greater amount of exposure.”).) And as Dr. Harlow recently explained, “in most situations” a “feature of causal relations in epidemiology and in the pathogenesis [of] cancer in particular is a monotonically increasing relation between measures of exposure and disease risk.” (4/9/24 Harlow Dep. 131:10-19.)

<sup>172</sup> *See, e.g.,* Mills, *Perineal Talc Exposure and Epithelial Ovarian Cancer Risk in the Central Valley of California*, 112(3) Int’l J. Cancer 458, 460 (2004) (Ex. 73 to Davidson Decl.) (reporting risks of 1.03, 1.81, 1.74 and 1.06 for ascending quartiles); Cook, *Perineal Powder Exposure and the Risk of Ovarian Cancer*, 145(5) Am. J. Epidemiol. 459, 463 (1997) (“Cook 1997”) (Ex. 74 to Davidson Decl.) (reporting risks of 1.8, 1.6, 1.2 and 1.8 across four categories of “cumulative lifetime days”); Rosenblatt, *Genital Powder Exposure and the Risk of Epithelial Ovarian Cancer*, 22 Cancer Causes Control 737, 740 (2011) (“Rosenblatt 2011”) (Ex. 75 to Davidson Decl.) (reporting risks of 1.21, 2.08, 0.87 and 0.87 across four categories of increasing lifetime applications).

downplay its significance. This, too, underscores the unreliable and results-driven nature of their Bradford Hill analyses.

**IV. THE OTHER BRADFORD HILL FACTORS DO NOT SUPPORT CAUSATION.**

Plaintiffs’ experts’ opinions regarding the remaining Bradford Hill factors—biological plausibility, specificity, coherence, analogy, experiment and temporality—are similarly unreliable and unscientific.

***Biological Plausibility.*** Plaintiffs’ experts generally posit that talc can move up the genital tract from the perineum to the ovaries (against gravity and the natural, downward flow of fluids in a woman’s body) and then cause ovarian cancer by inflammation. The Court previously reasoned that plaintiffs’ experts’ opinions were admissible because “Defendants ha[d] not introduced any evidence that this theory has been disproven as a matter of science.” *In re Johnson & Johnson*, 509 F. Supp. 3d at 175. As previously discussed, this approach erroneously “reverse[d] the burden of proof,” *see In re Onglyza*, 93 F.4th at 345, and is contrary to the more recent caselaw clarifying that biological plausibility requires more than identifying “[un]developed hypotheses.” *In re Acetaminophen I*, 2023 U.S. Dist. LEXIS 224899, at \*91.

But that is all plaintiffs’ experts have here. As explained in detail in Defendants’ Motion to Exclude Plaintiffs’ Experts’ Biological Plausibility Opinions, filed contemporaneously, there is no reliable evidence that talc can move

through the body against gravity and end up into the ovaries. Moreover, plaintiffs' experts have no reliable basis for their opinion that talc can cause ovarian cancer by inflammation. Instead, plaintiffs' experts recycle the same studies that they cited last time around, which are cherry-picked from a largely unsupportive body of literature, and cite a handful of new ones, primarily authored by now-withdrawn former expert Dr. Saed (who has been lambasted in peer review for his methods and conclusions). Both fall far short of providing reliable support for the theory that talc causes chronic inflammation or oxidative stress in vitro or in animals, much less in humans. And even if plaintiffs' experts could clear this bar, they also lack any reliable basis to opine that any observed changes in inflammation or oxidative stress markers lead to mutations or neoplastic transformation, much less to full-blown carcinogenesis.

***Specificity Of Association.*** “Specificity, in laymen’s terms generally means that an agent usually causes one type of human [disease]. When an agent is associated with a broad array of different types of diseases it weakens the evidence because it is non-specific.” *Gannon v. United States*, 571 F. Supp. 2d 615, 626 (E.D. Pa. 2007), *aff’d*, 292 F. App’x 170 (3d Cir. 2008). The proposed association in this litigation is highly ***unspecific*** because ovarian cancer is not a single distinct disease; rather, there are many different subtypes of ovarian cancer with different

points of origin and causes.<sup>173</sup> Presumably for this reason, many of plaintiffs' experts place little weight on the specificity factor,<sup>174</sup> or go so far as to claim the factor is "out of usage" because "some agents can . . . provoke multiple different pathologies."<sup>175</sup> However, just as statistical significance remains an important epidemiologic concept, specificity is far from moribund; in fact, its absence "highlights the complexity of the causation analysis." *In re Acetaminophen I*, 2023 U.S. Dist. LEXIS 224899, at \*86 (excluding opinion that specificity "factor is considered to be 'all but irrelevant' by modern epidemiologists").

In admitting the opinions of Drs. Carson and Clarke-Pearson, the Court accepted plaintiffs' claim that "the body of scientific evidence . . . demonstrates specificity with epithelial ovarian cancer, and more specifically, serous ovarian cancer." *In re Johnson & Johnson*, 509 F. Supp. 3d at 180-81. However, the core

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<sup>173</sup> Wentzensen & O'Brien 2021 at 202 ("Ovarian cancer is characterized by profound heterogeneity that can be observed in site of origin, genetic susceptibility, somatic mutations, molecular pathways, risk factor associations and morphologic differences.").

<sup>174</sup> (See, e.g., Kane Rep. at 34; Moorman Rep. at 37; Smith-Bindman 3d Am. Rep. at 36; Cote Am. Rep. at 36.)

<sup>175</sup> (Siemiatycki 3d Am. Rep. at 22; see also Moorman Rep. at 37 (downplaying specificity because "ovarian cancer has multiple causes"); McTiernan 3d Am. Rep. at 31 (similar); Dep. of Anne McTiernan ("8/19/21 McTiernan Dep.") 183:24-184:8, Aug. 19, 2021 (Ex. 76 to Davidson Decl.) ("Q. 'The identification of subtype specific associations would strengthen the argument for the existence of a causal relationship.' Do you agree with that? A. . . . You can have one carcinogen causing more than one type of cancer, more than one histotype of cancer. So it's not necessarily something -- it's not required for causality.")).

allegation in this litigation is not that talc only causes serous ovarian cancer; indeed, only two of the six bellwether plaintiffs have even been diagnosed with that particular subtype. As Dr. Cote made clear, epithelial ovarian cancer includes multiple subtypes, which she ***agreed*** are differentiated based on “the cell origin, molecular alterations, and clinical behavior.”<sup>176</sup> Notably, Dr. McTiernan conceded in another case “that an analysis of cancer risk where all cancers are combined[] ‘is not the accepted method of considering associations of carcinogens with specific cancer type risk.’” *See In re Zantac*, 644 F. Supp. 3d 1233 (citation omitted). As such, Dr. McTiernan’s practice of “commingl[ing] [of] data” from different types of cancer “depart[ed] from conventional science” in the Zantac litigation, *id.*, which is exactly what she and plaintiffs’ other experts have done in this litigation.

Lastly, some of plaintiffs’ experts assert that because uterine and breast cancer were not found to be associated with talc use in O’Brien 2024, this study provides “evidence of the characteristic of ‘specificity.’”<sup>177</sup> But the fact that plaintiffs’ experts agree that talc does not cause uterine or breast cancer does not

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<sup>176</sup> (3/21/24 Cote Dep. 26:12-19; Dep. of Rebecca Smith-Bindman (“10/1/21 Smith-Bindman Dep.”) 157:1-14, Oct. 1, 2021 (Ex. 77 to Davidson Decl.) (“Q. You agree that understanding ovarian cancer histological types is important because the risk factors, etiology and genetics of ovarian cancer, can vary by histological type; is that right? A. Yes.”).)

<sup>177</sup> (Siemiatycki 3d Am. Rep. at 54-55; McTiernan 3d Am. Rep. at 54, 99; Smith-Bindman 3d Am. Rep. at 36; Cote Am. Rep. at 36.)

change the far more pertinent fact that epithelial ovarian cancer is essentially a constellation of different cancers rather than a single distinct disease.

**Coherence.** Coherence means that “the cause-and-effect interpretation of our data should not seriously conflict with the generally known facts of the natural history and biology of the disease.”<sup>178</sup> In challenging the prior coherence opinions of Drs. McTiernan, Carson and Clarke-Pearson, defendants highlighted the absence of any animal studies showing that use of talc causes ovarian cancer and plaintiffs’ experts’ failure to reconcile their opinions with studies that have investigated the use of talc on diaphragms and condoms and found no increased risk. While the Court downplayed these arguments as “merely show[ing] disagreement with the conclusion on coherence drawn by the causation experts,” *In re Johnson & Johnson*, 509 F. Supp. 3d at 183, “conclusions and methodology are not entirely distinct from one another,” *In re Paraquat*, 2024 WL 1659687, at \*40 (citation omitted); *accord In re Acetaminophen II*, 2024 U.S. Dist. LEXIS 121259, at \*44 (same). In any event, defendants’ challenge was based on these experts’ failure to square these key scientific realities with their core causal theory, not a mere disagreement with their conclusions.<sup>179</sup>

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<sup>178</sup> Hill 1965 at 298.

<sup>179</sup> Defendants also pointed out that one feature all ovarian cancers have in common is that they arise as a result of genetic mutations, and there are no data to suggest that talc causes genetic mutations. See IARC Monographs on the

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Moreover, recent data that were not addressed by the prior experts or the Court have demonstrated that the talc/ovarian cancer association is not only incoherent, but defies common sense. For example, ovarian cancer incidence rates have declined each year since 1990, with rates decreasing by almost 3 percent per year from 2015 to 2019—a rate Dr. Clarke-Pearson agreed was “significant.”<sup>180</sup> This significant decline occurred while talcum powder products were still on the U.S. market.<sup>181</sup> It is incoherent to suggest that talc causes cancer, even though ovarian cancer rates have declined despite continued usage of talcum powder products. Additionally, a recent study by Dr. Moorman noted that although “genital powder use was more prevalent among African-American women,”

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Evaluation of Carcinogenic Risks to Humans, Vol. 93, Carbon Black, Titanium Dioxide, and Talc, at 411 (“IARC 2010 Monograph”) (2010) (Ex. 78 to Davidson Decl.). Although the Court reasoned that “whether a plaintiff’s ovarian cancer is caused by genetic mutations or use of talc[] is a question of specific causation,” *In re Johnson & Johnson*, 509 F. Supp. 3d at 182-83, that represents a fundamental misunderstanding of the issue. Both sides agree that **all** cancer involves genetic mutations. The question is whether talc contributes to those mutations or otherwise promotes carcinogenesis. The lack of any evidence connecting talc to genetic mutations underscores the incoherence between the proffered theory of general causation and what is known about ovarian cancer.

<sup>180</sup> (3/8/24 Clarke-Pearson Dep. 249:20-250:23; *see also* 4/4/24 Singh Dep. 48:17-21 (“[Q.] Do you agree with what it says here, that the incidence rate has declined by somewhere between 1 and 3 percent a year over the last 30 years or so? A. Yes.”).)

<sup>181</sup> (3/8/24 Clarke-Pearson Dep. 250:25-251:3.)

ovarian cancer rates are lower among African American women.<sup>182</sup> As Dr. Clarke-Pearson conceded, these incoherent results can only be explained by “talcum powder [not being] the only cause of ovarian cancer.”<sup>183</sup>

While plaintiffs’ experts find the coherence factor satisfied (with some even ascribing “considerable weight” to it),<sup>184</sup> none meaningfully attempts to explain how their theory of general causation can be reconciled with the data discussed above. Instead, these experts generally opine that coherence favors causation because it essentially mirrors biological plausibility.<sup>185</sup> As previously discussed and as elaborated in defendants’ separate motion addressing biological plausibility,

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<sup>182</sup> Davis 2021 at 1661, 1663-65; Dep. of Daniel L. Clarke-Pearson (“8/26/21 Clarke-Pearson Dep.”) 134:3-136:9, Aug. 26, 2021 (Ex. 79 to Davidson Decl.) (“Q. African-American women, to your knowledge, use talcum powder more than white women, true? A. That’s my understanding. Q. And on sheer rates of incidence, African-American women get ovarian cancer less than white women, right? A. That’s my understanding. Q. And that’s not what you would necessarily expect if talcum powder was causing ovarian cancer, right? [A.] So talcum powder isn’t the only cause of ovarian cancer.”) (objection omitted).)

<sup>183</sup> (8/26/21 Clarke-Pearson Dep. 134:3-136:9.)

<sup>184</sup> (E.g., Moorman Rep. at 37-38; Singh Suppl. Rep. at 22; Kane Rep. at 36.)

<sup>185</sup> (E.g., Kane Rep. at 36 (arguing that coherence is satisfied because consistency of association and biological plausibility are purportedly satisfied); Wolf 3d Am. Rep. at 20 (arguing coherence is satisfied because “[t]he findings and conclusions from epidemiological, animal, and in vitro studies are coherent with what is known about ovarian cancer”); Clarke-Pearson 3d Am. Rep. at 13 (similar); Cote Am. Rep. at 38 (arguing coherence is satisfied because biological plausibility is purportedly satisfied); Moorman Rep. at 38 (same); McTiernan 3d Am. Rep. at 101 (same); Singh Suppl. Rep. at 22 (same); Smith-Bindman 3d Am. Rep. at 38 (same).)

plaintiffs' experts' untested hypotheses regarding the purported mechanisms by which talc causes ovarian cancer are speculative and inadmissible. And even assuming the opinions on biological plausibility were admissible, they would not provide a basis for papering over the scientific realities discussed above regarding the declining incidence of ovarian cancer and data involving African American users of talc.

***Analogy.*** Plaintiffs' experts generally opine that the putative causal relationship between talc and ovarian cancer can be analogized to asbestos causing ovarian cancer, mesothelioma or lung cancer.<sup>186</sup> But plaintiffs' experts have no reliable evidence indicating that asbestos—at least at levels below heavy occupational exposure—causes ovarian cancer, as set forth in Defendants' Motion to Exclude Asbestos Opinions, filed contemporaneously. For this reason, the MDL Court's conclusion in the first *Daubert* ruling that “asbestos has been shown to cause cancer” and that “it is not unreliable for the experts to opine that because asbestos has been found in talc, it can similarly cause ovarian cancer,” *In re Johnson & Johnson*, 509 F. Supp. 3d at 184-85, should not be followed.

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<sup>186</sup> (E.g., Clarke-Pearson 3d Am. Rep. at 14; Kane Rep. at 13-14; Smith-Bindman 3d Am. Rep. at 38.) This factor does not appear to weigh heavily in plaintiffs' experts' causation opinions. For example, Dr. Siemiatycki states that “there is an argument for an analogy between talc and asbestos” (Siemiatycki 3d Am. Rep. at 75) and Dr. Smith similarly “would suggest the analogy of asbestos causing ovarian cancer and mesothelioma” (Smith Rep. at 21).

In any event, the proposed asbestos analogy is unreliable for other reasons as well. Asbestos and talc are distinct minerals with distinct chemical structures and morphology, and talc lacks the unique chemical and physical properties that make asbestos harmful—i.e., a fibrous shape, flexibility and durability.<sup>187</sup> Likewise, in contrast to asbestos, talc particles are normally plate-like and only rarely fibrous.<sup>188</sup> Plaintiffs’ experts’ conclusory opinions regarding the analogy factor fail to address these fundamental distinctions, or even to suggest what particular qualities of asbestos that make it dangerous are ostensibly shared by talc. These failures render their conclusory “analogy” opinions unreliable and inadmissible. *See In re Acetaminophen I*, 2023 U.S. Dist. LEXIS 224899, at \*92-93 (excluding proffered analogy of acetaminophen to valproic acid as a “bare assertion, unaccompanied by any discussion of the[ir]” respective chemical compositions).

**Experiment.** Hill also asks whether a causal relationship is supported by “experimental, or semi-experimental, evidence.”<sup>189</sup> Plaintiffs’ experts agree that

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<sup>187</sup> See *Glastetter v. Novartis Pharms. Corp.*, 252 F.3d 986, 990 (8th Cir. 2001) (per curiam) (“Even minor deviations in molecular structure can radically change a particular substance’s properties and propensities.”); *McClain*, 401 F.3d at 1246 (“even small differences in chemical structure can sometimes make very large differences in the type of toxic response that is produced”) (citation omitted).

<sup>188</sup> IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 100C, Arsenic, Metals, Fibres, and Dust (“IARC 2012 Monograph”) at 230 (2012) (Ex. 80 to Davidson Decl.).

<sup>189</sup> Hill 1965 at 298.

randomized clinical trials—the primary type of experimental evidence—have not been conducted on talc and ovarian cancer and that this factor is not satisfied<sup>190</sup> or they ignore it altogether.<sup>191</sup> To the extent plaintiffs’ experts do not even address this factor, that further highlights the unreliability of their approach to Bradford Hill. And to the extent plaintiffs’ experts opine that there are experimental animal and in vitro studies that support their causation theories,<sup>192</sup> they misread and cherry-pick the data, as elaborated in defendants’ motion addressing biological plausibility. *See In re Acetaminophen I*, 2023 U.S. Dist. LEXIS 224899, at \*112 (excluding opinion that experiment factor satisfied based on expert’s “highly inaccurate representation of the animal study literature”).

**Temporality.** Epidemiologists must also assess the “temporal relationship of the association—which is the cart and which the horse?”<sup>193</sup> Plaintiffs’ experts place “high weight” on temporality—i.e., emphasizing that talc use precedes an ovarian cancer diagnosis.<sup>194</sup> But even Judge Wolfson acknowledged that whether

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<sup>190</sup> (E.g., McTiernan 3d Am. Rep. at 101; Singh Rep. at 66.)

<sup>191</sup> (See, e.g., 4/9/24 Harlow Dep. 234:10-18.) Plaintiffs’ experts generally seek to minimize this factor. (E.g., Singh Rep. at 66 (experiment “weighted as less important”).)

<sup>192</sup> (E.g., Smith-Bindman 3d Am. Rep. at 38; Smith Rep. at 21; Kane Rep. at 36-37.)

<sup>193</sup> Hill 1965 at 297.

<sup>194</sup> (McTiernan 3d Am. Rep. at 99; see also Cote Am. Rep. at 37 (temporality is an “important” consideration in a causation analysis); Siemiatycki 3d Am. Rep. at  
(cont’d)

“[t]alc use precedes an ovarian cancer diagnosis . . . is ‘unremarkable’” on the issue of causation since “ovarian cancer typically develops late in life, whereas most women begin using talc by their mid-20s.” *In re Johnson & Johnson*, 509 F. Supp. 3d at 181. While the Court nonetheless reasoned that “[t]he weight to be given this factor is an issue for the fact-finder,” *id.*, that once again misapprehends the role of the Court as gatekeeper, *see Buzzerd v. Flagship Carwash of Port St. Lucie, Inc.*, 669 F. Supp. 2d 514, 530 (M.D. Pa. 2009) (“[T]emporal connection standing alone is entitled to little weight in determining causation.”) (citations omitted), *aff’d*, 397 F. App’x 797 (3d Cir. 2010).

In any event, “[t]he question is not whether the exposure precedes the diagnosis but whether it precedes the development of the” disease. *In re Acetaminophen I*, 2023 U.S. Dist. LEXIS 224899, at \*86-87; *see also In re Acetaminophen II*, 2024 U.S. Dist. LEXIS 121259, at \*74-75 (reaffirming principle). As Dr. Cote has recognized, temporality “can be . . . difficult to determine in diseases where there is a long latency period between the exposure and the onset of clinically apparent disease.”<sup>195</sup> If the latency of ovarian cancer is

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70, 73 (“[h]ighly important aspect[] in my weighting”); Singh Suppl. Rep. at 19 (“significant weight”); Smith-Bindman 3d Am. Rep. at 37 (temporality is “important” for consideration).)

<sup>195</sup> (Cote Am. Rep. at 37; *see also* Siemiatycki 3d Am. Rep. at 21 (temporality can be “difficult to ascertain with certainty”).)

as long as some of plaintiffs' experts hypothesize (up to 50 years),<sup>196</sup> it cannot be ruled out that ovarian cancer actually initiates *before* talc use in some women, which "would be fatal to a causal inference."<sup>197</sup> This is not merely theoretical.

"One advantage of the cohort study design is that the temporal relationship between exposure and disease can often be established more readily than in other study designs, especially a case-control design"<sup>198</sup>; however, the talc cohort studies have *not* observed an association between talc use and ovarian cancer, as explained above. *In re Paraquat*, 2024 WL 1659687, at \*39 n.58 (excluding expert's temporality opinion, which "completely ignores . . . a prospective cohort study that, by virtue of its design, would have controlled for temporality more effectively than any of the studies in his meta-analysis"). Accordingly, plaintiffs' experts not only overemphasize the temporality factor but also do not appreciate the very real possibility that this criterion is not satisfied.

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<sup>196</sup> (See, e.g., Clarke-Pearson 3d Am. Rep. at 13 ("[T]here is a latency period . . . that can extend over decades."); McTiernan 3d Am. Rep. at 61 (noting "the likely 30-50-year latency of ovarian cancer development after exposure to a carcinogen"); Wolf 3d Am. Rep. at 19 ("The average latency period between exposure to talc and diagnosis of ovarian cancer is at least twenty years."))

<sup>197</sup> (Moorman Rep. at 29.)

<sup>198</sup> *RMSE* at 558.

In sum, plaintiffs’ experts’ Bradford Hill analyses are “not an objective or rigorous application of scientific methodology.” *In re Acetaminophen II*, 2024 U.S. Dist. LEXIS 121259, at \*82-93. Instead, they are “result[s-]driven,” misread the literature and disregard longstanding epidemiologic concepts such as statistical significance. *Id.*

As the post-Rule 702 amendment cases make clear, such a misapplication of basic epidemiology is a matter of admissibility, not weight. *See id.* at 84 (“Had Dr. Ness’s opinion passed muster under Rule 702, it would be the jury’s duty to assess it.”); *see also In re Deepwater Horizon*, 2024 U.S. Dist. LEXIS 112817, at \*50-52 (“Dr. Elsner and Dr. Freeman did not ***reliably use*** epidemiology to conclude that substances associated with the oil spill can cause chronic dermatitis or eczema . . . .”) (emphasis added).

### **CONCLUSION**

For all of these reasons, defendants respectfully request that the Court exclude plaintiffs’ experts’ general causation opinions in their entirety.

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Respectfully submitted,

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